István Hargittai

CANDID SCIENCE II

Conversations with Famous Biomedical Scientists

Imperial College Press

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WITHDRAWN

Also by the same author

The Road to Stockholm: Nobel Prizes, Science, and Scientists, Oxford University Press, Oxford, 2002.
Candid Science: Conversation with Famous Chemists, Imperial College Press, London, 2000.
In Our Own Image: Personal Symmetry in Discovery (with M. Hargittai), Kluwer/Plenum New York, 2000.
Upptäck Symmetri! (Discover Symmetry!, in Swedish, with M. Hargittai), Natur och Kultur, Stockholm, 1998.
Symmetry through the Eyes of a Chemist (with M. Hargittai), Second edition, Plenum, New York, 1995.
Symmetry: A Unifying Concept (with M. Hargittai), Shelter Publications, Bolinas, CA, 1994.
The VSEPR Model of Molecular Geometry (with R.J. Gillespie), Allyn & Bacon, Boston, 1991.

Forthcoming

Candid Science III: More Conversations with Famous Chemists, Imperial College Press, London.
Candid Science IV: Conversations with Famous Physicists (with M. Hargittai), Imperial College Press, London.

Edited books

Symmetry 2000 (with T.C. Laurent), Vols. I, II, Portland Press, London, 2002.
Advances in Molecular Structure Research (with M. Hargittai), Vols. 1–6, JAI Press, Greenwich, CT, 1995–2000.
Spiral Symmetry (with C.A. Pickover), World Scientific, Singapore, 1992.
Fivefold Symmetry, World Scientific, Singapore, 1992.
Accurate Molecular Structures (with A. Domenicano), Oxford University Press, Oxford, 1992.
Quasicrystals, Networks, and Molecules of Fivefold Symmetry, VCH, New York, 1990.
Symmetry 2: Unifying Human Understanding, Pergamon Press, Oxford, 1989.
Stereochemical Applications of Gas-Phase Electron Diffraction (with M. Hargittai), Vols. A, B, VCH, New York, 1988.
Crystal Symmetries, Shubnikov Centennial Papers (with B.K. Vainshtein), Pergamon Press, Oxford, 1988.
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István Hargittai

Edited by Magdolna Hargittai

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Conversations with Famous Biomedical Scientists

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Foreword

More than ever before, the true stories of scientific discoveries are lost by the restricted space and style of the widely read journals and the hurried pace of reporting. There is no means of knowing either the personalities or the artistic qualities in the pursuit of understanding nature. Scientists look to the future rather than the past; they abhor writing and do it poorly. Autobiographical accounts are rare and the memoirs of the deceased in the volumes of the National Academy of Science (U.S.) and the Royal Society are commonly dull and impersonal. There is an important need to know about the people responsible for the progress of science as much as about those in politics, business, the military and the arts.

Oral histories can supply these much-needed accounts of how discoveries were made as told by those who made them. The success of this kind of historiography is attested by the enthusiastic reviews of István Hargittai's first volume, *Candid Science: Conversations with Famous Chemists.* This second volume, devoted to thirty-six biologically oriented chemists and chemically oriented biologists, is just as good. There is a fluency and intimacy, and hence readability, in the responses to questions from a knowledgeable colleague who had done his homework on both the scientist and the subject.

Hargittai poses questions that might not have been considered in an autobiography and that might have been frustratingly impossible for the author of an obituary memoir. Fascinating revelations emerge in the responses to questions that range from descriptions of the research subject, family background, inclinations to do science, religious beliefs and appraisals of other scientists, dead or alive. Even though I know many of the scientists,

some rather well, I learned things about each that were instructive and gratifying.

Among oral histories, there are book–length volumes, such as the current series on biotechnology conducted by the Bancroft Library of the University of California, designed exclusively for archival use. By contrast, this volume is a selection of hors d'oeuvres to be enjoyed by a wide readership. There are of course limitations to such brief oral histories. Leo Szilard once referred to "my version of the facts"; other versions would be helpful for clarifying the record.

All told, these unique volumes, and more that have been promised, are exceedingly worthwhile and can be enjoyed by all, young and old.

Stanford, California Arthur Kornberg

Preface

The science of the second half of the 20th century was dominated by the biomedical fields and this is expected to continue for the foreseeable future. The present selection of interviews gives a cross section covering a broad range of topics, personalities, and circumstances of recording. I prepared these interviews during the past few years. The volume includes two interviews by Magdolna Hargittai, my wife and fellow scientist who edited this volume.

The usual procedure of an interview is the following. After the recording session, I prepare and slightly edit the transcripts and they are corrected and revised by the interviewee. This procedure is repeated until the interviewee feels comfortable with the material. The finished product sometimes differs only in minor changes from the original transcripts, in other cases the changes are substantial. I see my role as a fellow scientist rather than that of an investigative reporter in these interviews. If the interviewee declines to answer a question, I drop the question from the published material. My experience is that this approach works better on the long run than highlighting any embarrassing situation. In a few cases I opted for compiling a profile on the basis of the conversation rather than having the interview format.

The first volume of my interviews, *Candid Science: Conversations with Famous Chemists*, was published by Imperial College Press, London in 2000. One with more chemists will follow the present volume and the fourth volume will feature physicists. The classification is admittedly loose and some of the interviews of the present volume could have appeared in other volumes. The interviewees in the present volume include physicists, chemists,

biologists, physicians, and others, by training, but they join conveniently under the biomedical label. About half of the interviews appear here in print for the first time and some of those that had been published before have been augmented.

I am grateful to all my interviewees for their patience and cooperation. I appreciate the illustrative materials from many of the interviewees, Ms. Kathy Bendo (daughter-in-law of George Hitchings), the Archives of the Laboratory of Molecular Biology in Cambridge, England, the Archives of the Cold Spring Harbor Laboratory in Cold Spring Harbor, New York, and the Archives of the California Institute of Technology in Pasadena, California. I express my special thanks to Edit Ernster of Stockholm for lending me images not only for the Ernster interview but for some of the other interviews as well. I appreciate the travel opportunities that our research and teaching provides and the family vacations that have been turned into interesting visits by these meetings and interviews.

Budapest, January 2001 István Hargittai

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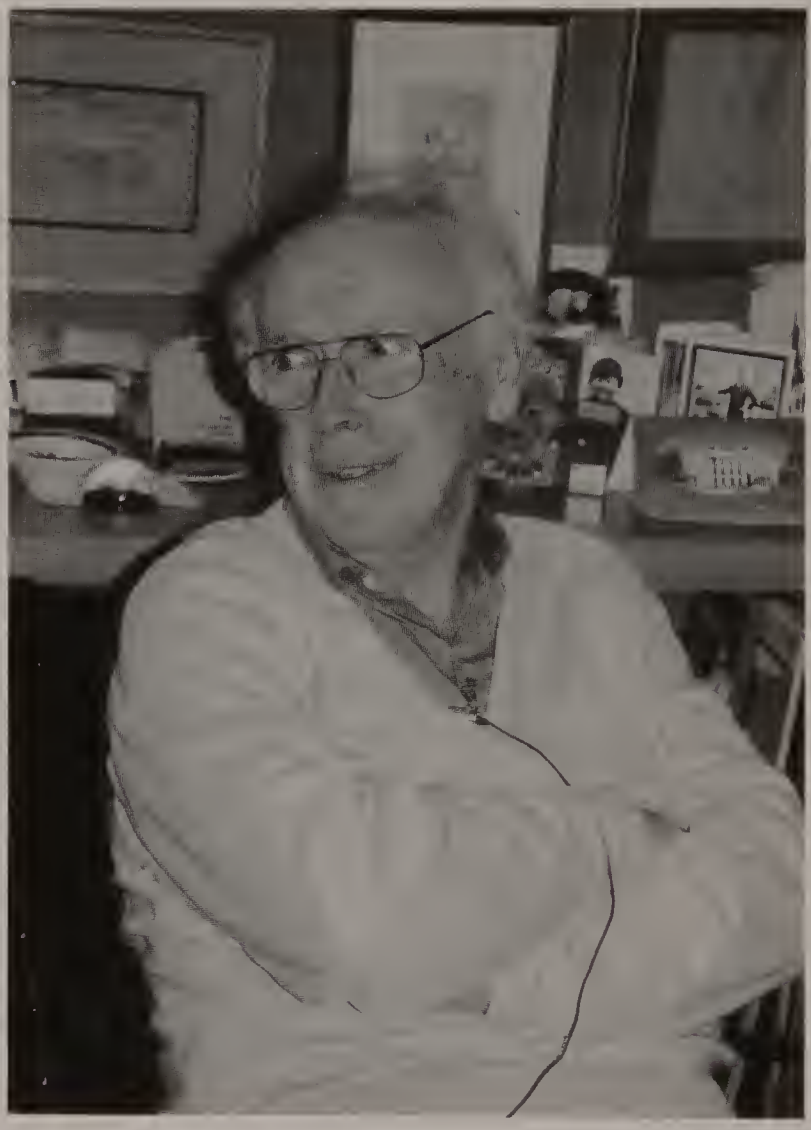


James D. Watson, 2000 (photograph by Magdolna Hargittai).

1

James D. Watson

James D. Watson (b. 1928, Chicago) is President of Cold Spring Harbor Laboratory in Cold Spring Harbor, New York. He is most famous for his discovery, jointly with Francis Crick, of the double helix structure of DNA in Cambridge, England, in 1953. Watson and Crick and Maurice Wilkins were jointly awarded the Nobel Prize in Physiology or Medicine in 1962 "for their discoveries concerning the molecular structure of nuclear acids and its significance for information transfer in living material." Dr. Watson's career included stints at the California Institute of Technology and Harvard University and from 1968 to 1993, he was Director of Cold Spring Harbor Laboratory. He was also the Director of the National Center for Human Genome Research of the National Institutes of Health from 1989 to 1992.

Fifteen years after the discovery of the double helix, Watson wrote a book *The Double Helix* [Watson, J. D., *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, The New American Library, New York, 1968]. This book has become a classic. Of course, it is only one version of the possible ways to describe the story. Watson himself stated in its preface: "I am aware that the other participants in this story would tell parts of it in other ways, sometimes because their memory of what happened differs from mine and, perhaps in even more cases, because no two people ever see the same events in exactly the same light." Dr. Watson's latest book is *A Passion for DNA: Genes, Genomes, and Society* [with an Introduction, Afterword, and Annotations by Walter Gratzer, Cold Spring Harbor Laboratory Press, 2000]. It is an essay collection, which contains many of Dr. Watson's introductory essays to the Annual Reports of the Cold Spring Harbor Laboratory as

well as more autobiographical pieces published elsewhere. In many of my interviews I ask the interviewee about his or her award-winning research. This is completely missing here in view of the so well known story of the double helix discovery. Some of my questions are rather sketchy. I just finished reading *A Passion for DNA* before the interview and I also tried to cover many topics in a limited time. My wife and I visited James Watson on a Saturday, May 20, 2000, that fit his busy schedule and it was also the last day of a visit of ours to the United States. We were heading to the airport from Cold Spring Harbor at the conclusion of the interview. It was a lively encounter, which I hope is conveyed in the following excerpts, which were finalized during a more relaxed visit by Jim and Liz in Budapest on July 21, 2000.*

What turned you originally to science?

I was curious of why the world is like it is? Laws of nature. Why did things happen?

Francis Crick (Nobel Prize, shared with Watson and Maurice Wilkins) and James Watson walk along the Backs, Cambridge, England, circa 1950. In the distance, the Kings College Chapel (courtesy of Cold Spring Harbor Laboratory Archives).

*This interview was originally published in *The Chemical Intelligencer* **2000**, *6*(4), 20–24 © 2000, Springer-Verlag, New York, Inc.

Any particular book or teacher?

There was a book about bird migration, which I got when I was seven years old, at Christmas. It made me interested in birds. My father had been a bird migration watcher for years. Then, when I got a little older, the question "What is Life?" became paramount. That objective, combined with my father's fairly strong anti-religious views, provided me the perfect background. I never had to rebel against my parents; I never had any crises over beliefs.

Have you been open about being non-religious?

Yes.

Isn't this rather difficult in the United States?

No, at least in university circles. When I was a child I was probably no different from Feynman, who also had a great antipathy to "truths" acquired by revelation.

What would capture a child's attention today to science?

The brain. How does it work? So many of its attributes are still unexplainable. What does taste mean? What is consciousness? How do you encode a system by which you like something or you don't like it. It's a very difficult problem.

How do you feel about classical training versus going right to the frontier? Following the double helix, Lord Todd congratulated you as an organic chemist when you were certainly not deep in organic chemistry.

He realized that our discovery was a chemistry discovery; it was not a discovery in biology.

Vladimir Prelog, not long before he died, ascribed the chemists' persistent staying away from DNA to the fact that chemists used to consider these systems to be dirty mixtures. So Lord Todd appears to have been exceptional.

In retrospect you may ask why wasn't Todd curious about what would DNA look like in three dimensions. At that time big molecules were largely for "colloid chemists." They were thought too big to study by conventional techniques of the organic chemist.

James Watson measuring a model of DNA in Cambridge, England (courtesy of the LMB Archives).

In your book A Passion for DNA, *Walter Gratzer says, "hunt for the genetic code was the most exciting period in early molecular biology."*

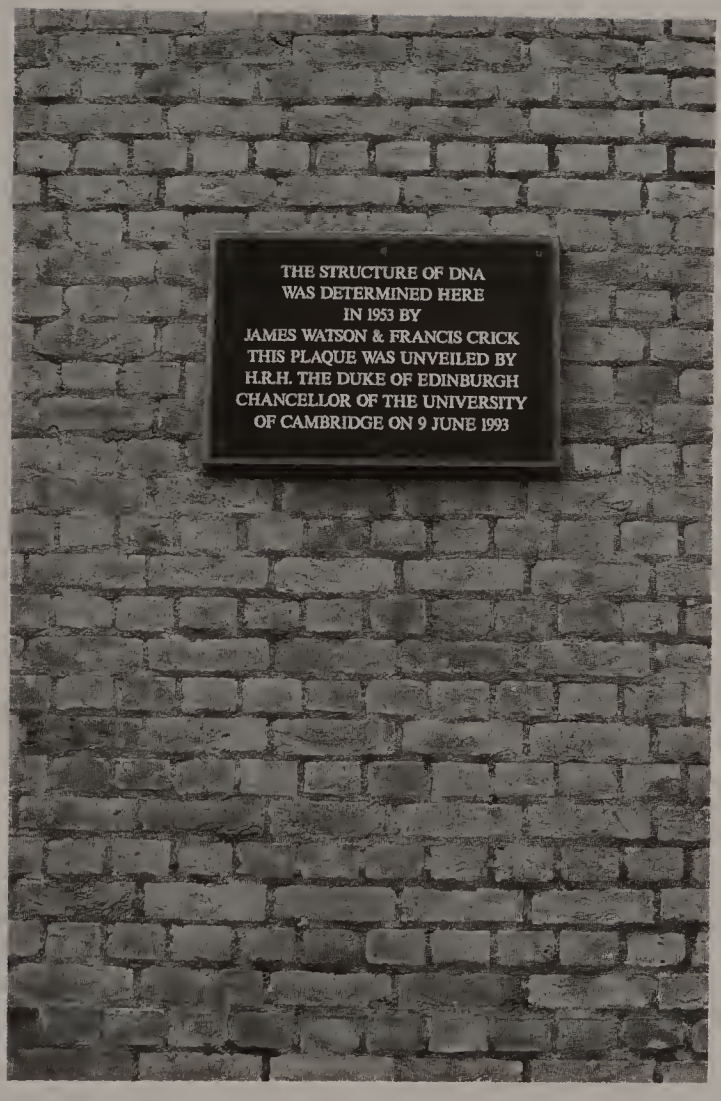
Yes, it was.

Was it really, or was it because you and a few other very influential people found it very puzzling?

No, no, it was. We wanted to know how cells read the information in DNA, so we had to know the nature of the information. And then to get to RNA you needed RNA polymerase, and then to make polypeptide chains you needed ribosomes.

Do you recall what happened with Marshall Nirenberg's paper in Moscow in 1961? Did people indeed rush out of the room, after its second presentation, to get home fast and repeat and continue Nirenberg's experiment?

The only persons who wanted to immediately repeat the Nirenberg experiment were Wally Gilbert and Severo Ochoa.



Plaque commemorating the discovery of the double helix on the wall of the old Cavendish Laboratory in Cambridge, England (photograph by I. Hargittai).

You don't mention Nirenberg in your book.

Nirenberg was very important and deserved his Nobel Prize but he was a biochemist whereas we always thought in terms of information.

What would be your longest ranging impact?

Probably my books. The discovery of DNA was just waiting to be made. It was not a difficult thing. Any good chemist focused on DNA should have found the structure of DNA. Pauling's failure to find the double helix was a very low probability event. But *The Double Helix* could not have been written by anyone beside myself.

Then there is The Molecular Biology of the Gene.

That also had a big impact.

There's a lot of chemistry in it. Did you learn that chemistry after the discovery?

Yes. You learn what you should know.

So it was not part of your training.

No, no, no. I liked natural history; I liked to be outside. In college I was largely interested in ecological successions. Then I thought I would be a professional naturalist.

So your legacy is your books.

Yes, and this institution.

Any pupils who carry on what you had started?

No. I had very good students but I don't ascribe their success to me.

You did not co-author papers with your students when you did not contribute to the work with your hands.

When I was in Indiana Luria didn't put his name on my paper, as he didn't do the experiments. Later I decided that that was also what I was going to do.

Because you didn't contribute to them manually?

Yes.

Doesn't this underestimate the intellectual contribution?

Maybe so but people work best when they're working for themselves.

Somewhere you said that Linus Pauling was isolated by his greatness. Are you isolated?

I'm not great.

But are you isolated?

No. Linus talked enthusiastically at people but not with them.

He seemed to me accessible.

No one called him by his first name at Caltech. As you know most Americans use first names.

Do people stop you for a chat?

Of course.

Intelligence and genetics: is this a taboo question?

For some people, yes. It's difficult to define intelligence while we don't really know how the brain works. I've always thought I have no mathematical ability and other people would say you have no mathematical interest and therefore you were not motivated to learn it. It's very hard to distinguish these alternatives. I think my brain works fast on what interests me.

You are saying, "The misuse of genetics by Hitler should not deny its use today." What bothers me in this is that any demagogue says a lot of things that have truth in its roots yet the total is entirely false. Couldn't we approach this whole problem without invoking Hitler and Nazism?

No, because when I go out in the public I'm constantly told, "You're playing Hitler." If other people didn't raise it I wouldn't, but they constantly want to talk about the "eugenic past." The German nation's failure to acknowledge the horrors of its eugenic past made it possible for their Greens to so long prevent it having a world class DNA-based industry. But abuse of genetics also had been identified with Stalin. He denied its existence. You had two extremes.

You have said that parents should have the right to terminate a pregnancy.

Yes.

That means, you would stop this possibility before birth.

If possible.

Not after birth.

Francis Crick gave a provocative lecture in 1968 at University College London where he said you should only be declared alive two days after birth. Later I have been mistakenly accused of that remark, ascribing to me Hitler-like motivations. Francis also then said the state should not spend any money for medical care about people above 80. Now that he is 84, he would probably disagree. He said this when he was 52.*

Would you subscribe to this two days after birth definition?

If we so acted, many families' lives would be inherently less tortured.

How could you set limits on such seemingly arbitrary deeds?

Best to let prospective mothers make all such decisions.

Reading your A Passion for DNA *you come through to me as very passionate about how genetic knowledge is used.*

Parents want to look forward to their children having happy futures. Recently there was much publicity about a prosperous couple in the

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* *In this connection I have asked Francis Crick in a letter about his current views. With Dr. Crick's permission, I am quoting from his response of June 28, 2001:*

I did indeed give a provocative lecture in 1968 (or thereabouts) at University College London, but I'm not sure that I still have a copy of it.

To reply to your two questions I would indeed modify my suggestions today. In the old days doctors quickly let a very deformed or handicapped baby die, rather than make exceptional efforts, as they often do now, to keep the baby alive. I now realize that it would be impossible, at least in this country, to count life as starting after the first two days of the baby's life because so many religious people believe life effectively starts much earlier, even at conception. In other words one has to consider not just the feelings of the baby (who hardly has any) but also the feelings of the parents, and of other members of society, however silly one may think them to be. But I do believe that doctors should not make exceptional efforts to keep a very handicapped baby alive.

As to the age limit, people now live longer than they did in the sixties, so I think such an age might be a little higher, but I doubt if a rigid rule would be acceptable. Again I think very expensive treatments, or ones that have only a limited availability, should be allocated in some sensible way. I've heard that the State of Oregon is trying out such a scheme.

If I were to give such a lecture again (which is unlikely) I would instead stress the right of a person who is incurably ill to terminate his life. I believe this is being tried out in Holland.

States who had a child with cerebral palsy. Initially they tried hard to accept that child but ended up taking their child to a hospital saying, "We can't handle it. We're incapable. It's beyond us." These weren't poor people, these weren't nasty people, but they were at their wit's end.

The Nazis carried out human experiments. If there are data applicable to today from those experiments, should they be used?

I'm not sure there is Nazi data of any value today. But if data still exist that would save someone's life, I would save someone's life.

Here's a practical question. The Nazis killed a lot of mental patients whose brains are still being preserved in Germany.

I doubt they have any scientific value today.

Then why don't they destroy them?

I would.

When people call you the Einstein of biology, how do you feel?

Very creepy.

It was obvious that the discovery of the double helix was to be rewarded by a Nobel Prize. But then it took almost a decade for the Prize to materialize?

Our Nobel became more than obvious after the Meselson-Stahl experiment showed that the complementary strands did separate. Before their seminal experiment, many biochemists remained reluctant to make nucleic acids as important as proteins.

Have you seen Erwin Chargaff lately?

I saw him about six years ago at some National Academy function in New York. Like many Central Europeans he thinks that important truths come from word games. I don't think they do.

But you also find language very important.

Having a rich vocabulary enriches your life while philosophy sidetracks you away from reality.

If you could meet any scientist from the past, who would that be?

There are obvious ones, Mendel, Darwin. I remain curious about Calvin Bridges, one of the great *Drosophila* quartet at Columbia. There was Morgan and his three students, Bridges, Sturtevant, and Muller. Muller was one of my teachers at Indiana, and I knew Sturtevant while I was a postdoc at Caltech.

It seems to me that the world is getting increasingly centralized. For science, the northeast and the southwest of the United States and Cambridge, England are at the top. Of course, I'm oversimplifying and exaggerating but when Manfred Eigen has something important to say he goes from Göttingen to La Jolla to talk about it and it is not the other way around.

We should keep science from being too centralized. In many cases it comes from governmental policies. French science has always suffered from Paris being too important. Luckily we have our Federal system by which the money is distributed partly on the basis of geography. You can do very good DNA science in almost all of our 50 states of the United States. America is prosperous and is putting even more money into science. Europe is not following in the same way. When I went to Cambridge, England, in 1951, its university was the best in the world.

Quite a lot of money is being spent on popularizing the Human Genome Project, its ethical, social, and legal aspects. What more could be done than what's already being done?

Right now it's not the misuse of genetics, rather the disuse of it, that worries me. We're, for example, not screening people for cystic fibrosis.

Why not?

There are three reasons. Firstly, most people are afraid to look into the future and possibly discover that they're carrying genes that could cause them harm in the future. Secondly, the Right to Life movement doesn't want genetic knowledge to be used for tests that might lead to abortions. Thirdly, many individuals, usually of leftist persuasion, believe that predictive genetic knowledge will lead to discrimination against victims of bad throws of our genetic dice.

During a Cold Spring Harbor Symposium, 1953, from l. to r., Max Delbrück, Alan Garen, Leo Szilard, and James Watson (courtesy of the Cold Spring Harbor Laboratory Archives).

Your longtime friend, Leo Szilard, had made his remarkable conversion from physics to biology just after the war. When Nirenberg made his discovery in 1961, he asked Szilard to sponsor his paper in the Proceedings of the National Academy of Sciences. *Szilard at that time had his headquarters in the lobby of the Dupont Hotel in Washington. Nirenberg spent most of a day telling Szilard about his discovery and in the end Szilard declined to sponsor it, saying that he was not a biologist.*

He made a mistake, a bad mistake. A year before I'd gone to Leo at the Memorial Hospital and told him about the evidence on messenger RNA and about the ribosome. It was late March or the first day of April and Leo said he didn't believe it. Leo was consumed by that time with the bladder cancer. Was it only one high school in Budapest that produced Szilard and the great intellectuals of his peer group?

That's a myth. There were several high schools and two in particular. There was also a strong Jewish upper middle class. Szilard, Wigner, Hevesy, Teller, and Neumann didn't all go to the same high school.

James Watson in his office with István Hargittai, Cold Spring Harbor Laboratory, 2000, during the interview (photograph by Magdolna Hargittai).

Elizabeth and James Watson in the Budapest City Park, 2000 (photograph by I. Hargittai).

If a person like Leo Szilard would show up tomorrow at your doorstep, would you be able to recognize his potential, would you give him support, a place?

Possibly not, because he was always two steps ahead of everyone else. When you go so fast, it threatens people. Hopefully today the equivalent of Leo exists somewhere worrying about how the brain works. Occasionally I say I have a Szilard idea. I'm most pleased with myself until I come down to reality realizing that most clever ideas do not reflect reality.

Money is often a big motivation in life. Today even graduate students in molecular biology think about selling their science.

I was never brought up with money as a value. It was ideas that mattered.

What did your father do?

He collected money and not very successfully.

Not a very pleasant occupation.

No, it was terrible.

Your mother?

She ran the personnel office at the Red Cross in Chicago during the war. Later she worked in the office of admissions of the University of Chicago. She wasn't an intellectual like my father was. She was a people person while my father liked ideas. For him ideas were the main thing and in that sense I had a semi-Jewish upbringing.

Did you realize this at that time?

No.

You have expressed your sympathy with the underdog. Who is the underdog today?

The Europeans. They are not moving fast enough to make it seem necessary for very many younger Americans to spend part of their educational experience in England or on the continent.

Maclyn McCarty, 1997 (photograph by I. Hargittai).

2

Maclyn McCarty

Maclyn McCarty (b. 1911) is Professor Emeritus at The Rockefeller University in New York City. He graduated with an A.B. in biochemistry from Stanford University in 1933 and with an MD from Johns Hopkins University in 1937. He worked with Oswald T. Avery (1877–1955) in the early 1940s on the transforming principle. Their research culminated in the publication of the paper by O. T. Avery, C. M. MacLeod, and M. McCarty, "Studies of the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types," *Journal of Experimental Medicine* **1944**, *79*, 137–158. This work showed for the first time that DNA is the genetic material.

Dr. McCarty published a book about the research leading to the discovery, *The Transforming Principle: Discovering That Genes Are Made of DNA* [W. W. Norton & Co., New York, 1985]. In his subsequent career at Rockefeller, from which he retired in 1981, Dr. McCarty was involved in research on C-reactive protein, the biology and immunochemistry of *streptococci*, and the nature of rheumatic fever. Dr. McCarty is a Member of, among others, the National Academy of Sciences of the United States and the American Academy of Arts and Sciences. His many honors include the Robert Koch Gold Medal, the Wolf Prize, and the Albert Lasker Special Public Health Award. Our conversation was recorded in Dr. McCarty's office at The Rockefeller University on March 11, 1997.*

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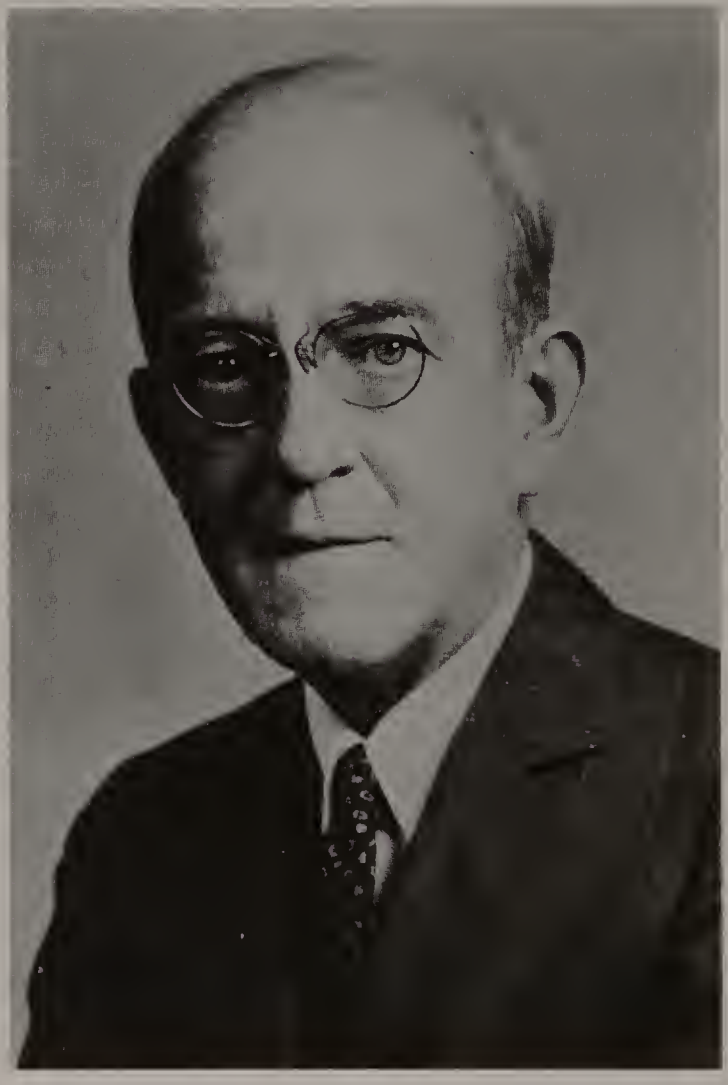
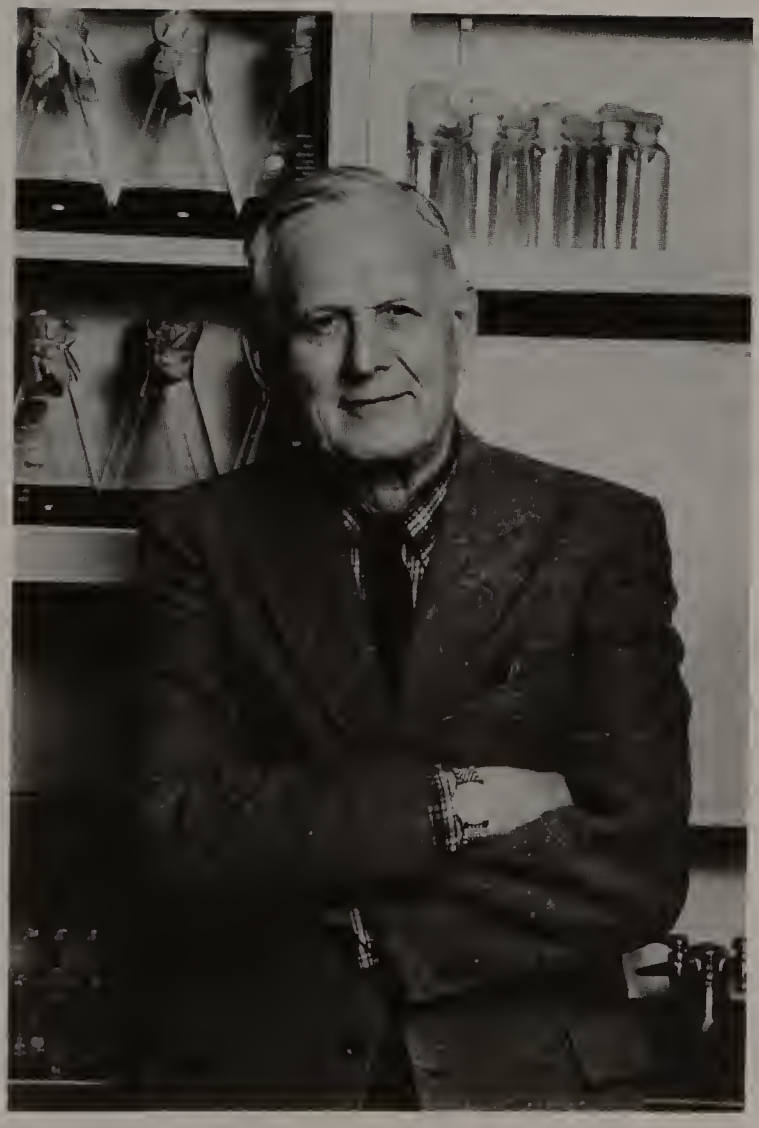


Oswald T. Avery (courtesy of Maclyn McCarty).



Maclyn McCarty in 1982, at the time of his writing the book *The Transforming Principle: Discovering That Genes Are Made of DNA* [W. W. Norton & Co., New York, 1985] (courtesy of Maclyn McCarty).

Just a few days ago, the world learned about the sheep cloning in Scotland. Would you care to comment on it?

I don't have the concerns that people have about it, nor do I feel terribly surprised. They had to solve a technical problem to achieve it. It was getting the nucleus from the donor into the ovum under the right conditions so that it would go through the process of ordinary development. They failed in any number of attempts, and only one came through. You can see that there are still uncertainties about it. It was perfectly reasonable to try it, and therefore I am not overwhelmed.

Do you consider it a direct continuation of your work?

In a sense. There is an awful lot of what you call "direct continuation," because there was no knowledge of what genes are made of at the time we published our work. The whole story of the DNA development has come about since then. It was dependent primarily on knowing what you're dealing with, knowing that it is DNA that is carrying genetic information.

Time *magazine portrayed Watson and Crick as the ones who introduced DNA into science.*

This is not uncommon. What Watson and Crick did, of course, was come up with the structure of DNA, which involved important implications about its functions. It had a profound impact, but it is unlikely that they would even have done the structural work without our evidence on the genetic role for DNA. It depended on knowing that first, and everything that has happened since all comes from that. I consider the Watson-Crick paper one of the major steps after our discovery, almost 10 years later. But a lot of things had been done in the intervening period to enhance the evidence we had that DNA was the genetic material.

Was there any single important step?

Rollin Hotchkiss, for example, worked with Avery until Avery retired and continued afterwards. Our experiments had dealt with one character, and that was the organism's polysaccharide capsule. Hotchkiss looked at several other characters. Thus, he showed that two kinds of antibiotic resistance could be transferred with DNA. He also worked with an enzyme and showed that DNA from a cell that had it could transfer it to one that did not have

Maclyn McCarty with James Watson and Francis Crick in La Jolla California, in 1977, at the time Dr. McCarty was given the First Waterford Biomedical Award (the vase in front of him) (photograph by Robert Smull — The Lensman Photography, San Diego, California, courtesy of Maclyn McCarty).

it. This work broadened the base of the evidence pointing to the general validity of our discovery. In the system of pneumococcal transformation, you could transfer any number of traits with DNA.

How do you assess the contribution that Erwin Chargaff made between your discovery and the elucidation of the double-helix structure?

His work began fairly early after our paper. He was one of the minority who believed its conclusion at the outset and was motivated to change his line of work to a study of the composition of DNAs from various sources. DNAs had been considered so simple and uniform in composition that they could not have the specificity required for gene function. Chargaff showed that they were certainly not all alike, but varied widely in base composition, and the demonstration of base pairing was very useful to Watson and Crick in their structural studies.

Did you have any direct interaction with him?

No. It's possible that he talked to Avery, but I don't believe that we knew what he was doing until his first publication on the subject. He has always

acknowledged that it was our paper that led his doing that work. Then when we recently celebrated the 50th anniversary of our discovery, he participated in the affair, and we had a chat at that time. He has always expressed himself negatively about Watson and Crick.

What was the most important discovery that your work was building upon?

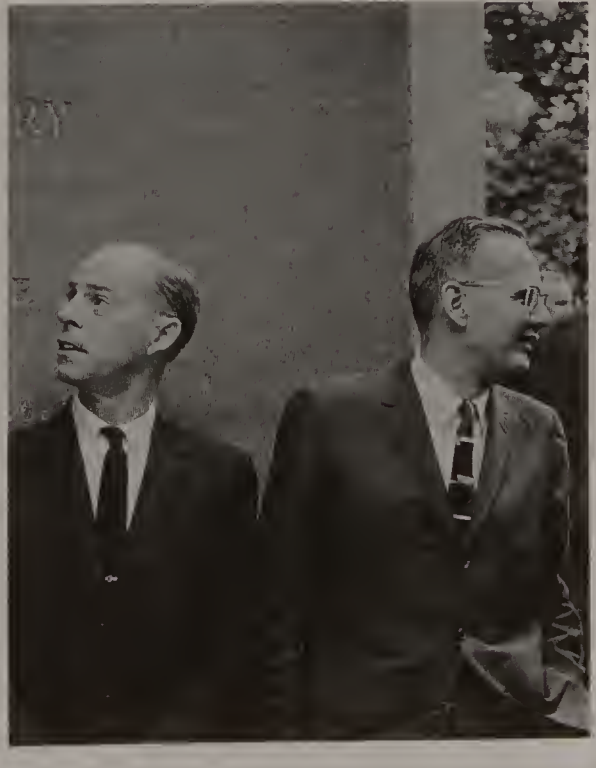
It all started with work on pneumonia. It was Fred Griffith in London who had received numerous sputum samples from patients with pneumonia for bacteriologic diagnosis, and he had become interested in the fact that many of the samples from patients contained four or five different pneumococcal types. Each of these would have a different capsular polysaccharide. He didn't think it was likely that patients had acquired four or five different types and entertained the idea that some interchange of type was going on in the living individual. He set up experiments that were actually designed to look at this in the mouse. He heat-killed *pneumococci* of one type and put them into the mouse with a small inoculum of living *pneumococci* that came from a different type but lacked a capsule. When the mouse died, the organisms recovered had the polysaccharide capsule of the killed *pneumococci.* He followed this up with a number of such experiments and reported the results as the transformation of pneumococcal types. He assumed that the heat-killed cells were releasing something that would stimulate this result. He did not think about it genetically, at least he did not say so. He thought about it as something that came from the heat-killed cells that the living cell used to make the new polysaccharide. This was in 1928, and this was the beginning.

Griffith's experiments were repeated in a couple of laboratories, one of them in Germany, at the Koch Institute in Berlin. Here, in Avery's laboratory, Martin Dawson also repeated the work. It was clear to everybody that it was not the survival of the heat-killed cells but that something else was going on. Dawson then succeeded in getting transformation to work in the test tube, without the use of the mouse.

The next person to work on this problem in Avery's laboratory was Lionel Alloway, who showed that transformation could be achieved using cell-free extracts rather than heat-killed cells. His work was published in two papers in 1933 and 1934, and, from that time, one had the material that made it possible to find out what the active transforming substance was. It was not easy, however.

Colin MacLeod started working with Avery in 1934. He struggled with it for three years, making some progress. It was a difficult system, and he had to give it up because he had no publications from his laboratory work after three years. Another difficulty was Avery's illness that kept him away from the laboratory for a considerable time.

In the meantime, the point of view about the work had changed. Initially, the interest was in pneumonia and its control. The capsule had been shown to be very important in the disease. Pneumococcal cells without a capsule were rapidly ingested and killed by white blood cells and thus did not cause disease. Initially, there was some thought that transformation experiments might help in finding out how the capsule was being synthesized and provide information that would be useful in devising means for control of pneumonia. But as they worked with the transformation system, MacLeod and Avery began to think about what was going on, that is, about the change in the living cell. They found that when they took the cells that had been transformed and now made a capsule that they had never made before, the active transforming material was reduplicated in the cell in addition to the continued production of the new capsule. This comes close to the definition



Colin M. MacLeod (1909–1972) on the left and Maclyn McCarty at the dedication of the Avery Memorial Gate in 1965 (courtesy of Maclyn McCarty).

of a gene. This gradual recognition really determined Avery's drive to find out what the stuff was.

MacLeod did other things in the lab from 1937 to 1940, and he and Avery agreed to get back to the job in the fall of 1940. In the course of this renewed effort, MacLeod was offered the position of Chairman of the Department of Microbiology at New York University (NYU) Medical School. He was told that he better take it, because there was no opening for him at Rockefeller, since a replacement for Avery, who was soon to reach emeritus status, had already been selected. He left in July 1941. That year I was working at NYU with a former Avery person, William S. Tillett. Tillett had been at Rockefeller for eight years in the 1930s. He helped get Avery to accept me in his laboratory on a National Research Council fellowship that I had just been awarded. This is how I came here in 1941, right after MacLeod had left.

Avery was 64, and the retirement age was 65. He became emeritus at 65 but stayed on. He was dependent on somebody being with him. It didn't take long for me to start working with him, and I picked up where MacLeod had left off, continuing to pursue the nature of the substance that was in these extracts.

Could you then summarize the work from 1941 on, resulting in the 1944 publication?

Let me say first that what MacLeod had done earlier was very important. For example, you could take these extracts and deproteinize them by shaking with chloroform, a method for deproteinizing biological materials that had been worked out years earlier. Many other things had also been established. The first recognition that DNA was a constituent of the extracts had come in January 1941. This was kept in mind during the subsequent work, but reproducible fractionation procedures proved difficult to devise. In June 1941, MacLeod was writing up the status of the experiments prior to his departure. He indicated that maybe if you got rid of the polysaccharide, which was there in fairly large amounts, you would eliminate the activity. This was not because they thought that the polysaccharide was the transforming substance but because it might have to be present as a template to initiate the synthesis of new polysaccharide.

In the Avery lab, they had a soil bacillus that produced an enzyme that would split the polysaccharide of type III, which was the type being used in the experiments. My first task was to completely eliminate the

polysaccharide from an extract, using this enzyme, to see what would happen. The obvious result was that it made no difference; the transforming activity was not affected by getting rid of the polysaccharide. That made us realize that we ought to get rid of it in order to purify the product. When we did this and treated the extract with alcohol, there was still a large amount of fibrous precipitate, which had been attributed to polysaccharide. This turned out to be DNA. So we began focusing more on DNA, and the next experiments that supported the possibility of its importance were carried out with the ultracentrifuge.

We found that the active material in these extracts was of high molecular weight. It would deposit rapidly in the lower part of the centrifuge chamber. We were testing the material both chemically and for transformation, and the evidence was mounting that the only component that concentrated with this high-molecular-weight fraction was DNA. We did other experiments, such as electrophoresis, and the behavior of the material was again fully consistent with the notion that the active substance was DNA. The focus of our work then shifted to getting a fraction free of other detectable components and containing only DNA.

Although MacLeod was at NYU at the time, he kept his interest in the work. He came back early on to teach me the handling of large amounts of bacteria. We grew organisms in hundreds of liters of medium and prepared several lots of relatively pure substance with elementary analysis consistent with DNA and little evidence for contamination with protein or other substances by a variety of tests. This is how we finally came to our conclusion in the Spring of 1943, and started working on the publication. Avery, at his customary summer retreat in Maine, worked on the Introduction and Discussion and put together the experimental part, going back to the early work of MacLeod as well as my own. We finished the manuscript in the fall and got it to the editor of the *Journal of Experimental Medicine* in November 1943.

Coming back to your experiments and handling large amounts of bacteria, were there safety precautions?

Indeed there were. If you had a fine mist coming out of the centrifuge, you had bugs all over the place. A technician in the lab developed a protecting housing around the centrifuge, and steam was used for sterilization before opening the housing. Then we handled all of the materials with towels soaked in a germicidal solution and heat-killed the bacteria at 65°C for

30 minutes as soon as they had been removed from the centrifuge cylinder and placed in suspension in salt solution. After that, we did not have to worry about infectivity.

Apart from the initial interest in pneumonia, would bacteria have been the most convenient subject to study in any case?

The key is not the bacteria, the key is the phenomenon of transformation, which just happened to be in bacteria. It was the first model providing a test for genetic activity. The geneticists of those days worked with various techniques, but none of their procedures would lead to a test of the chemistry of the process. The final recognition that transformation was possibly a model for genetic transfer is the point. There wasn't any model before.

When you determined that DNA was the transforming principle, was it assumed that it had universal validity?

The reason that you would at least assume the possibility that it was universal was because it was already known that the chromosome is where the DNA is. This suggested right away that this was a possibility.

Didn't you feel an urge to go on with this research?

That's the question that I have thought a fair amount about. The activities that we were engaged in were different from what was needed next. I was an MD as were Avery and MacLeod, and I had gone to Medical School with the intention of doing disease-related medical research. And this is what I had done before, and this is what the Avery laboratory was about as well. I continued working with Avery until 1946, that is, two years after our 1944 paper. We worked to substantiate the idea that we were dealing with DNA; for example, I isolated a purified DNAase and demonstrated that it was highly potent in destroying the activity of transforming DNA. We thought about next steps, what variation between nucleic acids must depend on. And I think it is just as well that I did not continue in this direction. None of my training was in the direction of structural work. Then, in early 1946, I got an offer to take over the laboratory for streptococcal infection and rheumatic fever at Rockefeller. I was trained as a pediatrician and had seen a lot of rheumatic fever, and we knew that it was somehow related to streptococcal infection, but we didn't know how. So here was a problem that certainly was up the alley

of what I wanted to do, plus the fact that it would give me a permanent position. From then on, I closely followed what was going on in DNA research without getting involved in it again. And this is probably just as well.

Is it correct to say that the main opponent to accepting your discovery was Alfred Mirsky of The Rockefeller Institute?

Yes. He took the view that you really couldn't tell whether you had as much as 1 percent protein in the DNA preps. That would have been millions of molecules. I don't know what motivated him, but he was very vocal about this. His opposition was well known in the biochemical community and in the cell biology community.

He was working in a laboratory two floors above us. He had gotten the nucleoprotein from mammalian cells by a very nice technique. Nucleoprotein is soluble in 1 M salt solution. If you bring the salt concentration down to the usual 0.14 M, it all precipitates out. He could purify it from other things this way. He thought he could extract our *pneumococci* with salt. It turned out that very little stuff was extracted. We had worked together on an experiment, in which we took one of our large batches and went through the salt procedure. We got a little bit of this fibrous precipitate on bringing the salt concentration down. I tested it, having some trouble putting it into the solution, but it was active in transformation. However, in some way or other, Mirsky thought that this experiment was an important step in our process, because he wrote some time later that it had led us to wash our cells thoroughly before we would proceed with extraction. But this was not the case as I had been prewashing the cells for a couple of years, since we first realized that we didn't need the polysaccharide; we washed the cells to get rid of it before we tried to get rid of the remainder with an enzyme. So this was a misinterpretation on his part, and he thought we were ignoring his contribution, which was really that one experimental collaboration. He had also provided us with some of his pure mammalian DNA, which was helpful. Actually, I had the idea of reporting the experiment with Mirsky in the paper, but Avery vetoed it. Mirsky was widely enough known, and vocal enough, and influenced a lot of people. It took him a long time to come around. About 25 years later, he wrote an article in *Scientific American* in which he cited our work with *pneumococcus*, and in this article he seemed to accept our findings of 1944. Thus he knew it later.

Did he ever say he was sorry?

No, never.

*In the book about Nobel and the Nobel Prize [*Nobel: The Man & His Prizes, *3rd edn., The Nobel Foundation and W. Odelberg, Eds., Elsevier, New York, 1972, p. 201], it is said "it is to be regretted" that the discovery of DNA being the transforming principle was not awarded the Nobel Prize. This is quite an unusual and unique statement. Did the discovery belong to chemistry or to physiology or medicine?*

I think because of the biological activity involved in it, it's more likely to have been in physiology or medicine. It is hard to say, though, because biochemical fractionation played a major role in it.

Let's get back to your own history.

I was born in 1911 in Indiana. When I was growing up, we were moving around because my father was in the automobile business. I was in Portland, Oregon, for a while and started school there, then went back to Indiana, and finally to Wisconsin. I went to Stanford University for undergraduate studies and got my degree in biochemistry. I went to medical school at Johns Hopkins because I thought that it was where you went if you wanted to do medical research. I specialized in pediatrics and started doing research in infectious diseases. But it was always my intention to get into the laboratory when I had finished my practical training. This is what I did when I got to New York.

How did you become interested in chemistry?

Four of us in our high school set up chemical laboratories in our basements. We had a club, "Amateur Chemists." This was in Kenosha, Wisconsin. Only one other of the four of us went into science. My mother told me that by the time I was 10, I told her I was going into medical research. The chemical aspect was something I was interested in, and so I took the biochemistry training before medical school.

Did you read Paul de Kruif's Microbe Hunters*?*

I had already made my decision before the book came out, but I read it, and it further stimulated my interest. However, it did not initiate it, and I really don't know what did.

Any other interests?

I have been interested in history and in science history. When I was putting together my book, I realized that there were a lot of things I did not really have any solid evidence about.

Can you tell us something about Oswald Avery?

He was not a very outgoing person. He was a small man who was quite restrained, at least by the time I got to know him. He was a lifelong bachelor. At the time I knew him, he no longer liked to talk in public. We induced him to talk at our regular staff meeting in December 1943. By then, our paper was in press, but he had not talked there for years. He was President of the Society of American Bacteriologists the year that I came to Rockefeller. He gave the Presidential Address, and he would not let it be published. Talks of this kind were not science, and he just didn't want his general comments in print.

So he was known as a reserved person, somebody who would not rush to publish.

There is no doubt about that.

Then shouldn't Dr. Mirsky have had a difficult time convincing people that Avery's publication may have been premature?

He was talking to a different group of people, not to bacteriologists. The geneticists and the cell biologists didn't know so much about Avery.

Was Avery's reservedness in disseminating the discovery frustrating for you?

Obviously there was some frustration, but he was a very likable person and quite revered around here; and everybody looked out for him, particularly since he had been ill. He had hyperthyroidism, a disease in which the thyroid overworks. They had to operate and take out a considerable part of his thyroid gland. He was ill for years, and people were very solicitous about it, including MacLeod. Avery had a tremor, which comes with this illness, and he could not do experimental work anymore, and he got quite depressed at times. He was just recovering fully in the late 1930s.

The Rockefeller Institute, later, Rockefeller University, has produced strong lines of research in your area and related areas. Any comment on this?

The early leadership was very strong. The hospital started a little later, in 1910, and its first director was Rufus Cole, who selected people like Avery. The leadership of the Institute and the hospital did a very careful job, and the time was also ripe for building up a strong institution.

It all started with John D. Rockefeller, Sr., the man who originally accumulated the fortune. He had an adviser, Frederick Taylor Gates, who had been a Baptist minister. This man read a book on medicine by Sir William Osler in the 1890s. Osler was a Canadian who came down to the U.S. and was involved with the building of the Johns Hopkins Medical School. He had written a famous textbook on medicine. Gates read the book and realized that there were so many instances in medicine where you could only describe the diseases but could do nothing effective about treating them. This is why he persuaded Rockefeller to set up an institute for medical research. It was organized in 1901. It was very strong from the very beginning.

Do you anticipate that it will continue to be as strong?

Obviously, times have changed. The support for research for the first 50 years came totally from endowments. It was after World War II, in the early 1950s, that federal support began, with the National Institute, later, Institutes, of Health. It was not until the mid-1950s that I had to start thinking about external support. The number of people engaged in biomedical science today is probably between a hundred and a thousand times as many as it was in our early days. At that time, there were very few places where one could go, and Rockefeller was one of those few places. It's an entirely different situation today.

Are your children aware of the DNA discovery?

My oldest son is 61; he is a physical chemist who worked more in chemical engineering and is now retired. My second son is Head of Biology at Johns Hopkins. My third and much younger son, born in 1958, is named Colin Avery McCarty. I also have a daughter and eight grandchildren. I think they are all aware of the DNA discovery. One of my nieces taught biology, and when this came up in the textbook, she would say, this is

my uncle. She got laughed at by her students; they didn't believe her.

Did you get recognition, the three of you, for your discovery?

Not the three of us — not together. However, I did this work when I was young, and there was the Eli Lilly award in bacteriology and immunology, and Avery nominated me for this prize. The age limit was 35, and I got it just before I turned 35, specifically for the work on the transforming principle. The highest recognition I got was the Wolf Prize, in 1990.

You started a whole new career when you were 35. Were there any comparable achievements in your research after the discovery of the transforming principle?

Our goal was to discover the mechanism of how streptococcal infection causes rheumatic fever, and it was never reached fully. It has not been reached yet. This goal seems to be much harder to reach than the one in the DNA study. But we did contribute a lot of things to the problem, and our laboratory was recognized for its contributions.

Joshua Lederberg, 1999 (photograph by I. Hargittai).

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Joshua Lederberg

Joshua Lederberg (b. 1925) is University Professor Emeritus and Sackler Foundation Scholar at The Rockefeller University in New York City. He got his B.A. degree from Columbia College in 1944 and his Ph.D. from Yale University in 1947. He was Professor of Genetics at the University of Wisconsin (1947–1959) and Professor of Genetics and also of Biology and Computer Science at Stanford University (1959–1978). He was President of The Rockefeller University between 1978–1990. Dr. Lederberg shared the Nobel Prize in Physiology or Medicine in 1958 "for his discoveries concerning genetic recombination and the organization of the genetic material of bacteria." (The other half of the Nobel Prize was shared by George W. Beadle and Edward L. Tatum "for their discovery that genes act by regulating definite chemical events.")

Dr. Lederberg has been a Member of the National Academy of Sciences and a Foreign Member of the Royal Society (London) and received the National Medal of Science, just to mention a few of his numerous distinctions. He has taken on also a large number of public responsibilities.

Our conversation was recorded in Dr. Lederberg's office at The Rockefeller University on March 9, 1999.*

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Your record is so impressive that it is hard to decide where to start my questions. I would like to get an overall picture, however impressionistic, of your career.

This is why I gave you the web site, http://profiles.NLM.nih.gov. The record is all there.

Of course, but I can't assume that all our readers will have read it.

When I was writing my own memoirs, I was becoming very frustrated about the amount of research I'd have to do on my own papers. Finally, I decided that it was more important for me to put my papers in order than to try to get to a bottom-line answer to your question "Who is this creature, Joshua Lederberg?"

Why don't we start with some family history?

Somewhere about 1850, the whole family on my father's side, three generations of Lederbergs, left Plock, Poland, and went to Jerusalem. Plock should be distinguished from the Ukrainian town called Plotsk, which is where Ben-Gurion came from. Plock is about 100 kilometers west of Warsaw on the Vistula River, an area that was contested between Russian and Prussian influence. As far as I know all the Lederbergs are connected with this region. There were great rabbis as part of my paternal tradition, but the family alternated between rabbinical and business interests. My mother's side is much more devout. My brother believes he can trace our lineage back 10 generations to R. Dov Baer, the Maggid of Mezritch, closely connected with the founding of Hasidism. My mother's family came from the center of Hasidism in Israel — the town of Safed.

My father was orphaned at a fairly young age. He was a brilliant seminary student. His uncle gave him an opportunity to study in America and he went to what is today the Yeshiva University, somewhere around 1920. Then he went back to Palestine and married my mother, and they settled in the United States in 1924. I was born in 1925 in Montclair, New Jersey. I regard myself as part of the melting-pot tradition. I was a very good American and grateful for the opportunity that America would have to offer. It was a matter of balancing respect for my traditions and lineage and assimilation into a very modernistic American way of life. My father was an orthodox rabbi. He practiced in Washington Heights, here in New

York City. I was raised in New York City, went to public schools, notably Stuyvesant High School, which focused on science, and then, by virtue of a scholarship, went to Columbia College. By the time I was 17, I was a sophomore at Columbia, and America had just entered the war. I had the opportunity to enroll in the Navy and to compete for officer training programs. I was enlisted in the Navy on July 1, 1943, and was very lucky to be allowed to continue my premedical training. I worked some months as a parasitologist in a hospital of the Navy. I remained in training throughout the war.

How much were you aware of what was going on in Europe?

I was very well aware of it. My parents were strong Zionists and were deeply concerned about what was happening. I don't know that we had the details of the Holocaust. I was 8 at the time of the burning of the Reichstag in 1933. I remember the news of it very vividly, with horror about the possibility that the democracies of the West were not able to mobilize themselves in order to prevent this demon from overtaking them. I studied the politics of the situation very closely. It has marked a great deal of my existence. This is one reason I have been interested in international relations and national security questions — to be sure that we never make such terrible mistakes again.

The United States did not measure up to Great Britain in taking in refugees, especially children.

No, I understand that and my father was quite an activist in this regard. I was too young. We did see some number of German Jews who did come to work in the part of New York where I grew up. There was a joke about calling them the "Fourth Reich." They were a culturally well-settled group, they had given up a lot in order to leave Germany. So the answer to your question is, I was very aware. It was part of my determination that if I ever reached a position of any influence, I would at least put in the analytical efforts to try to understand what the implications of certain courses of action might be. For example, in 1943, there was the Casablanca conference. At that time President Roosevelt enunciated the policy of demanding unconditional surrender from the Germans, with the implication that their national existence would be crushed. I was shocked at what I thought was very clumsy statesmanship because I felt

that would only unify whatever dissident groups there might be within Germany; instead, it would be much better to do things that would divide the German people from their tyrant. I think such a policy could have ended the war years sooner and it could have had enormous consequences with what happened with the Holocaust. And the historical reality was the crucial role that the U.S. played in the reconstruction of a democratized Germany.

Concentration camps, or the railroads to them, could have been bombed.

One could have some arguments about that, but I was not in a policy-making position. I was an 18-year-old at the time. I know the grievances about a failure to take more direct action; but one also has to recall the restraints under which Roosevelt and the other leaders were operating. Roosevelt was very proactive in leading this country into the war. If his opponents had been able to use that doctrine, they'd have driven him out of office. Roosevelt was conducting war against Hitler in the Atlantic long before war was declared, in ways that today would be described as unconstitutional. Roosevelt was operating under very severe political constraints. There was a very large constituency in the Midwest that was against England, against the war with Germany, felt we should not be involved in any way; for this to become the war to save the Jews would probably have destroyed Roosevelt's effectiveness in mobilizing the country. With respect to the bombing of Auschwitz, it's very easy to say but there could have been enormous negative repercussions. Suppose, Auschwitz had been bombed and Jews had been killed by American bombs even if they were on their way to the gas chamber. What a thing Hitler would have been able to make out of the fact that we were bombing helpless people who were there in concentration camp just to work. Bombing the railways would have been totally ineffective. Those railways would have been repaired within a matter of days. It was not an optimum use of U.S. air power. I think a much greater mistake was Casablanca, that is, the policy of unconditional surrender. But not taking the refugees is absolutely obscene, that degree of inhumanity, to turn the ships back. I'm not offering any extenuation for that, quite the contrary. Hopefully, we are in a state of continued moral evolution. An optimist might foresee that many acts (or neglects) that we shrug off today will be condemned tomorrow.

Returning to your story...

I started at Columbia in 1941, I graduated from the undergraduate college in 1944, and started medical school in October 1944, but I continued my research project that I had started with Francis Ryan on *Neurospora* in his laboratory at Columbia College on the campus at 116th Street. The medical school is at 168th Street.

When did you become aware of Avery et al.'s discovery that DNA is the transforming principle and what was its impact on you?

It had an enormous influence on me, which I have documented. But to answer your first question first, I had probably heard about it even before it was published. Although Alfred Mirsky has been criticized for being so negative and being so skeptical, at the same time he was the herald, he was the person who was carrying the news of it to many, many people. He was pointing to the work and said, "Look, these people are doing this work, they make these claims that DNA alone is sufficient for the transforming activity. I, Mirsky, am skeptical about that, it's very difficult to be sure that there isn't some residual quantity of protein and that the protein is the active factor." It was a perfectly legitimate position. I don't think he should be criticized for maintaining that skepticism. He maintained it for a long time, and we may say too long, but it was important to maintain some degree of resistance in order to evoke a response. The response was: Mac McCarty did a wonderful job in piling up one bit of evidence after another that really nailed it down for sure about the purity of the material. You could not be absolutely sure until DNA was synthesized. As long as you were preparing DNA from a natural source, you could always argue that there was also some molecule of something else that was contaminating the DNA and was the source of specificity. There was no way around that. When Khorana and Kornberg synthesized DNA, we could be really quite certain that it was just DNA and DNA alone that was sufficient. In 1952, there was the Hershey-Chase experiment, and in 1953, there was the X-ray structure of DNA (Watson and Crick). They didn't add any more evidence as to whether it was DNA but made it plausible, the physical model of how replication could take place. By about 1955, there was nobody arguing with it.

In 1944, I was a student at Columbia. Mirsky was collaborating with one of the professors at Columbia (A. W. Pollister) and there were frequent

communications, many seminars, so I knew about the paper by the time it was published. We had a reprint of the article, though not the journal. The *Journal of Experimental Medicine* was up at the medical school. I also have a written record because I was so impressed by the article that I wrote a note about it on January 20, 1945, and that I have saved and it's on the web site. There are not many contemporary records that people wrote down that that was their view but I've been in a long-standing argument with Gunther Stent about the reception of the Avery story. That web site, again, http://profiles.NLM.nih.gov, documents every element of that argument.

I was not the only one who was influenced. In terms of who changed research directions, what was there to do? There were two questions. One, was this pure DNA? Or was this some contaminant? The assay system was quite arcane, and very few people who were not already experts on *pneumococcus* would have been willing to try to repeat those experiments themselves. First of all, it's a dangerous organism to work with. Second, the recipes that were published for how to deal with it were very complex in the early days. I would have been very reluctant to try to attempt a direct repetition unless I had the opportunity to actually work for a while in the Avery laboratory. That lab closed down within a couple of years after their report, Avery died in 1955, and that was another reason that slowed down the diffusion of the experiment *per se*.

The other question was, here is a phenomenon but is it really the gene? It's a very specialized story, it had to do with one trait, the capsule of polysaccharide. For a long time, there were many people willing to believe that this was a phenomenon of seeding, of having a template for the aggregation. There were other examples of it. If you use starch phosphorylase with glucose 1-phosphate, you need a little starch as a starter in order to get the assembly, in order to get the polymerization into starch. So other polymer syntheses were known that needed polymer starters. One could have argued that that's what this phenomenon was, maybe it needed some nucleic acid as a kind of a coenzyme, so other interpretations were possible in addition to the one that this really was the gene. That was the question I wanted to address to really nail this down because I did see that here was the beginning of what was by then called genetic chemistry and everybody now calls molecular genetics. We needed to solidify the two pillars: One, is it DNA? What's the chemical identity? And, two, what's the phenomenon in the biological sense? Is it really gene transfer? Neither

of those was totally solidified by the observation of this one case, of this one organism, of this one trait, in the *pneumococcus.*

Chargaff went after the chemistry of the DNA, and it was a very important contribution to break down the dogma of the 1:1:1:1 relationship of the tetranucleotide structural hypothesis that Levene had developed here at The Rockefeller Institute. He had made many important contributions but the best thing he was able to do about the structure was to conclude that it was either a tetranucleotide or a tetranucleotide polymer because of the approximate uniformity of the ratios of the bases that were present in his DNA preparations. When Chargaff demonstrated that DNA was not 1:1:1:1, we began to see that there was more room for variety of internal structure. That made much more plausible the possibility that nucleic acids could be the carrier of genetic information.

On the other side, if this was a gene, my first thought was that we needed to get a transformation in an organism whose genetics had already been worked out. I thought *Neurospora* would be a very good candidate for that. I had already been working with Ryan on mutants of *Neurospora.*

Ryan had been a postdoctoral fellow with Beadle and Tatum in 1941–1942 at Stanford. He was their first postdoctoral fellow after their initial publication in the fall of 1941 on biochemical mutants in *Neurospora.* Ryan learned the technology and the ideology of biochemical mutations at Stanford and brought that back with him to Columbia. I met him when I was a sophomore in the academic year 1942–1943. I'd heard about him from other people around the department and it struck me that this is the work I really wanted to do. I gave him no option but to accept me in his laboratory. I was a real pest.

Beadle and Tatum and you shared the Nobel Prize in 1958. Ryan was still alive. Had there been a fourth person included, would it have been him?

It's imaginable. If he had been a more aggressive personality, he might have made sure that he was a coauthor. He was not the originator of the idea of using genetic recombination, but it started in his laboratory. But instead of his aggregating it to himself, in a very self-denying way he suggested that I continue the work in Tatum's laboratory. So I brought that idea to Yale with me in 1946 with Ryan's very active encouragement. I had already done the first experiments looking for recombination in Ryan's laboratory.

When I came to New Haven in 1946, I'd already made a proposal to Tatum; see that letter in the web site also, outlining the experiment. Tatum was also a self-effacing personality and I'd never learn whether he'd thought to do this kind of experiment himself with strains he'd actually furnished. One of the advantages of going to Tatum was that he'd already produced some of the kinds of mutants that were absolutely crucial to doing the experiment that I wanted to do. Both Ryan and Tatum were extremely generous to me in a very non-postmodern way. Tatum personally did none of the experiments. He did provide the crucial strains for them and he provided an atmosphere that made it possible to continue the work and he did all the other things, arranged for my funding and so on. He did everything a laboratory head could do and more.

Did you have any interaction with Erwin Chargaff?

I met him at the Cold Spring Harbor meeting but did not have direct contact with him as a student. I read his autobiography not too long ago, and it gave me great compassion about the strains that he had been under in many ways. I should probably get in closer touch with him.

He played a very crucial role. He was also very obstinate about many things. He refused to acknowledge that ribose had been proven to be the pentose sugar in what we now call RNA. He insisted to call it pentose nucleic acid because the sugar had not been isolated and crystallized and paper chromatography was not a sufficient criterion of chemical identity for him. This meticulousness was very important in getting the numbers right in terms of the composition but it could lead him into other complexities. He was so fussy about his analytical work.

Were your experiments successful from the very beginning?

The experiments with *Neurospora*, to try to transform an organism genetically, failed. They would have failed anyhow; it was many years before people learned how to treat fungi so that they could be transformed. They also failed because of a methodological obstacle. I was trying to transform a leucine-dependent mutant to one, which would grow in the absence of leucine. I got positive cultures but I also got them in the controls without the extracts (hopefully) containing DNA, which was the best I could say about them. This was an artifact and I realized that one needed a sharper

system to be able to do it. This could go in two directions and I decided then to concentrate on *E. coli*, instead of trying to find a nonbacterial organism in which to do transformation, to see if we could get sex in bacteria to make it a genetic organism so that DNA transfer experiments could have a genetic interpretation. That led me to try the experiments on genetic recombination in *E. coli*. Remembering the artifact I got when I was using a single mutant from *Neurospora*, I realized that I would have to use doubly marked strains in order not to have the artifact of reverse mutation in one locus interfere with the result. In the end this was the reason that I went to work with Tatum, because he had doubly marked strains that he had already prepared. In those days it meant a lot of painstaking work.

I started my work at Yale in mid-March 1946; by the middle of May, I had positive results, and by the middle of June, I was absolutely certain. I'd repeated the crossing experiments a dozen times, many variations, segregation and recombination of unselected markers, multifactor crosses. The Cold Spring Harbor Symposium was being held in 1946 about the 4th of July. Tatum was scheduled to give a paper there and I managed to be smuggled in as an extra onlooker. During the course of the symposium, it was obvious that things about recombination were very much up in the air and so Tatum and I decided to disclose these experiments. We got permission from Demerec, who was running the symposium, to have an extra half-hour to present the results. I called that a disputation. I got into a debate with André Lwoff about the robustness of the experiments — that I'd done all the controls needed. That was a very lengthy discussion. It was very fortunate for me to be able to have this presentation before such a large and critical audience because the issues could be hammered out right then and there. People were under the discipline that they were there and other people knew that they were, so it was possible to bring the debate to closure. If this had been simply a published article, people could have sustained their skepticism for a long time, have had questions in their mind, and even though I could answer them, without having the place to put these questions, they would have remained up in the air. That kind of confrontation is a very important sociological event. It was not before my peers, it was before my seniors, I was a 21-year-old among all the giants of the field. Of course, I had Tatum's authority to go along with. The only real holdout was Max Delbrück but that was chronic. He was a skeptic about many, many things, so I shouldn't take it personally.

From 1946 to 1958 — it took the Nobel Committee 12 years to recognize your discovery.

That's reasonable. It would not have been possible for five years, because it would have taken that long to have it reasonably accepted within the inner circles of the scientific community. I think that in five years the geneticists who understood the experiment were pretty unanimous about it. For the older-line microbiologists, people who write the textbooks, it took about 10 years before the textbooks were corrected about sex in bacteria. Had the award come sooner, that would have meant not only that it was accepted but that it would have shot to the top in priority. There were a lot of other things to give prizes for.

Was this your most important work ever?

I think so. Right next to it is the discovery of viral transduction, consummated along with Norton Zinder, my first graduate student. It was his doctoral dissertation in Madison, Wisconsin. He came into my lab, also from New York City, in 1948, with a recommendation from Francis Ryan. I had already been working with *Salmonella* and gave the cultures to Norton. We were looking for recombination in *Salmonella*. It is a similar kind of organism to *E. coli*; they are taxonomically quite closely related. I thought we would find the same thing. Instead, very different things happened. I was very skeptical of Norton's early positive findings for quite a long time before I realized that the phenomenon his experiments were showing was not the same thing. That was a diffusable agent, something that could be filtered. When you grew two cultures together, something appeared in the filtrate and the filtrate would be able to change the genetic characteristic of the target organism. It eventually turned out that that substance was a bacteriophage. One strain was leaking a bacteriophage that would attack the other one growing on the other one, it would carry bits of genetic material that could be filtered, you could get bacteriophage preparations that would then transmit bits and pieces of DNA to a target organism. It was a totally new phenomenon of genetic transfer. In some respects it is even more iconoclastic than conjugation. Conjugation merely says that there is sex in lots of organisms and there is also sex in bacteria. Transduction says that there's a method of genetic transfer for which there was no precedent prior to that time, that viruses can pick up DNA and transmit it to target organisms. I might even say that transduction even eclipses recombination.

This whole constellation of work on methodologies for studying genetic exchange, doing genetic mapping, putting the genetics of bacteria onto a reliable and robust basis, was my most important work, and most of my work was connected with that.

Would any of your work translate into biotechnology?

All of it, eventually. The industrial uses were very slow to come. As early as 1950, I was consulting with the Bristol Laboratories about improvements in penicillin production and I tried to introduce them to using genetic methodology for strain improvement. They listened to me but hardly did any of it. It was DNA splicing that turned the corner for industry. In DNA splicing I was scooped by Stanley Cohen. I was working on it but he had a much clearer insight into it and worked out much more elegant experiments than we.

You got into administration during your Stanford years.

I didn't find medical genetics so I decided to build it. It is hard to convey this today when genetics is so central. Every issue of the *New England Journal of Medicine* has an article and every other issue has a lead article in this area. That was unknown in the 1950s. Genetics was not even taught in many medical schools.

Then came the Presidency of The Rockefeller University.

It was a very special opportunity. I was interested in building new programs. I was becoming more and more of an integrator; even my own research was going more and more into what is the methodology of science. I was spending at least half of my time in epistemological and computer science research at Stanford. I've always been interested in the methodology of science, I was very successful at a young age and also wanted some understanding. Why? What were the best methods of achieving the most rapid progress? I also developed an interest in computers as analogues of organisms. They were complex systems subject to algorithms, capable of evolution, obviously much simpler than organisms but one should be able to learn a great deal about how to relate structure and function by looking into the details of computers. When computers became accessible to academic communities, around 1960, I became very actively involved. My suppositions proved to be correct — it was very illuminating to dig into how they worked.

I was more interested in that than in what to do with them. I invented things to do with them in order to have an excuse to remain connected with these quasi-organisms.

Did you interact with Carl Djerassi at Stanford?

I got to know Djerassi while we were recruiting him to Stanford, and we found we had overlapping interests in biotechnology. He and I founded the Syntex Institute for Molecular Biology in 1961, with funding from the Syntex Corporation. Carl had invited me to be a consultant to Syntex and I had visited him in Mexico City. At that time he was commuting between Stanford and Mexico City, which must have been very exhausting for him. So I'd suggested to Syntex that the mountain should move to Mohammed and that Syntex ought to move its laboratories to Sanford Industrial Park. I had also suggested to start thinking about how to commercialize advances in what we now call biotechnology. So Syntex funded the initiation of an institute. Its early emphasis was nucleotide biochemistry, similar to George Hitchings's works on some of the modified bases. The art of manipulating DNA was barely getting started by then. Very good people were enlisted for this new institute, but although Syntex supported it well, it was also obvious that it was not the centerpiece of the company. Eventually, all the work gravitated into doing steroid chemistry. Our original intention was premature and we weren't quite ready yet for DNA splicing. A few years later, this institute was reintegrated into the rest of the Syntex organization.

Another area in which our interest overlapped with Carl's was that I had become interested in exploiting space missions to look for biology outside the Earth. I coined the term exobiology to initiate that as a discipline. Starting in 1961, NASA offered to fund an instrumentation laboratory, which I directed at Stanford. We helped to put together the Viking mission to look for life on Mars. This required a deep analysis of what are the criteria of life, what are the most efficient methods of recognizing it, what if it's not quite like terrestrial life, and so on. I was convinced that one common denominator would be organic molecules. I also thought that chirality would be a strong evidence of life. We even had something named the Pasteur Probe. I became interested in mass spectrometry as the most versatile analytical methodology that could be used for characterization of organic molecules. Of course, Carl was already using it in his natural products work. So he and I collaborated in the development of mass-spectrometric analytical tools that might be

adapted for the Viking mission. In the end, the MIT group was willing to undertake much more arduous engineering work, actually adapting instruments that went into the Mars spacecraft, and eventually they got the contract.

Another question was data analysis. We thought it would be a good idea to build in as much local intelligence as possible because of the 12-minute communication time between the Mars and the Earth. Our idea was to enable the spacecraft to make local decisions, by building into it some local intelligence. I got into artificial intelligence (AI) and we ended up with computer-operated mass spectrometry together with built-in interpretation, including the deconvolution of the mass spectra into organic molecular structures. Here I was trying to emulate Carl Djerassi on the computer! We did build the first computer-controlled GC-MS complexes and Finnigan commercialized those. Quite apart from the conceptual impetus it gave to the Mars experiments, it had some other useful outputs as well.

It was also my introduction to AI and to epistemology. There was a scheme built into our complex for the generation of hypotheses. In this case the hypothesis was the organic molecular structure, but one could generalize that for other cases where you have a theorem to explain a set of data. This is beautiful in its simplicity. The theorem is the structure that you're postulating. The modes of generation of all possible structures, how you constrain them, how you both expand the trees to generate all the instances and contract them by pruning them at a very early stage, when you so contrive the generator that you can confront it with data capable of falsifying the direction you're in at the earliest possible stages, and so on. As you see, I'm using an epistemological language to describe a computer program. That shows how they became unified and also how I became more and more interested in ways of thought, how one might be able to assist human imagination, try to understand it better, and to facilitate the actual development of scientific doctrine.

You have been involved also in Eugene Garfield's projects. I noticed recently that you chair the Editorial Board of The Scientist.

Our interactions go back to the founding of the Institute for Scientific Information and his bibliographic tools for retrieving scientific data. I've always been interested in trying to discover smarter interfaces so that you can discover existing literature by similarity of concept rather than

by similarity of strings of characters. Garfield had a brilliant idea using the citation linkage as a step in that direction. It gives a sense of connectedness. The scientific literature is a network, and the emergence of citation analysis is putting more of a sense of obligation to report your sources because they will be used in this way. They will also be used to locate your own production in the world of ideas, as well as of getting recognition and so on.

Did all these activities signal a diminishing interest in your original field of research?

I was obviously broadening my interests away from the laboratory. Frankly, the field that I had helped to start had grown so explosively that, having been one out of one or one out of two people with any knowledge of interest in it at the beginning, I became one out of thousand or tens of thousands. It became increasingly difficult for me to identify an area where I could feel, "What's going to happen if I don't do this experiment?" If the answer was that somebody else would do it, that is not a very impelling motive in my point of view. I've never been motivated by just being the person doing something first. I want to be the person who thought of something that nobody else would've thought of. So I was looking for a different set of arenas of activity with that principle in mind. I think it's also an optimizing principle about how to best use one's intellect.

When you came to The Rockefeller University, what was your agenda? Was it just to keep up this institution?

The agenda was a very conservative one. You put it exactly right. I have said that many times that it was an institution of the type, quality, and character that was disappearing from the American scene and I was going to try to hang on to it in a very strong way. The Rockefeller University was just the right size. It did medical research in a broad sense — it covered all the biological disciplines. It was very important that everybody on campus could have a meaningful discourse with everybody else and yet not be constrained within "You're a pharmacologist, You're a biochemist" and so on. That was my vision in my dream. It's only imperfectly true. It does not have the independence of resources to free its members from the need to look for funding outside.

In this respect, there seems to have been quite a change over the years. Bruce Merrifield was able to go on for years with his pioneering research without worrying about funding and publishing while he was working on his discovery of solid-state protein synthesis. Today this wouldn't seem to be feasible.

The endowment has remained more or less fixed while the institution grew enormously, mostly with the influx of federal funds. The ratio of claimants to internal resources became much larger. I still tried to protect that tradition as much as I could, and I hoped to have enough unrestricted resources while I was President that I could allocate them if I could recognize a Bruce Merrifield to at least enable him to continue. I did that; I did it imperfectly, and it became more and more difficult as time went on. But it was still within the margin of possibility when I first arrived at least.

Did the original mission change when The Rockefeller Institute became a university?

Not really, although Det Bronk wanted it to. He was going to generalize it to a broad-scale graduate university, but that was an aborted experiment. He thought there was an infinite source of Rockefeller money in it. It soon became obvious that there was not. The Rockefeller University is still a very focused institution of biomedical research. We have the attributes of a graduate university but we do not have a law school and we do not have an undergraduate college, and we don't even have a medical school though we collaborate with Cornell Medical College in that regard.

The preeminence of The Rockefeller University in its own field has decreased over the years but this was perhaps inevitable.

Of course. When The Rockefeller Institute was founded, its budget was 40 percent of the national expenditure of medical research. Today it's under 1 percent.

Is it usual for a President to stay on in the same place after his term?

Yes, making sure that he is not a nuisance. I've been very careful about that. My predecessor is also still here. I've also started my lab and it's been in operation. I've great trouble getting funding for it, but I have a couple of benefactors who keep it going.

What's your current research interest?

I'm going back to cell fusion in bacteria and its consequences in *E. coli* so I'm really going back to my original work of 1946. There are still many unsettled questions about those phenomena.

You also record interviews with other scientists.

I've been interested in the historic biographical process. It's part of understanding science and it's part of my trying to understand my own career.

Who are your heroes?

When I was a child, Albert Einstein and Chaim Weizmann were my heroes. Of the scientists today, whom I would try to emulate? There are so many of them. I see people in much more detail now. I wish I could be an Einstein in the profundity of his thinking; I don't think I've reached that level of abstraction; I was a little lazy in developing my mathematical skills. My molecular-biology work reached its peak at Wisconsin, and though I continued to make creditable contributions, they don't compare with the previous ones partly because the field had enlarged so substantially and it was hard to find unique things to do. I had innovations in other areas, and the DENDRAL work was in a different field. It ended up being an experiment with negative results but we did a respectable job in the Viking mission. I've made some theoretical contributions, in immunology in particular. I've been analyzing the kinetics and evolutionary aspects of infectious disease, and also connected with it were policy issues. I'm spending a great deal of my time today on trying to make sure that we're well mobilized to deal with both natural outbreaks and with malicious ones, with bio-terrorism. I'm in Washington one or two days a week, mostly on issues connected with those matters. Even though the cold war is over, there are still many, many dangers on a smaller scale.

Do you see any danger of a genetic war?

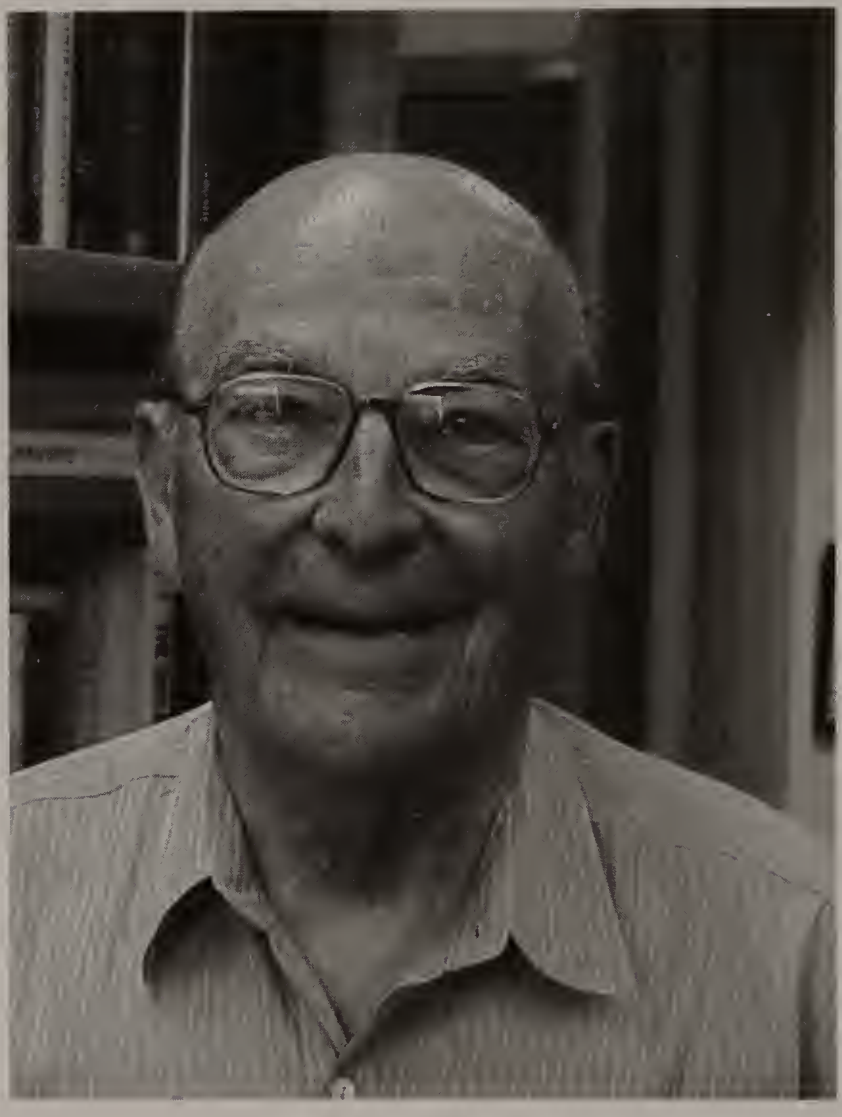
No, it doesn't fit, humans aren't organized along genetic lines. If you look at the DNA of people, you'll find it so heterogeneous that it makes such an idea a fantasy.

Any message?

Look at the details is the message. The message is in everything I've said.

AFTERTHOUGHTS

I began my scientific career with the view that scientific enquiry would dispel myth and superstition and enable a deeper, realistically founded insight into human nature, our place in the universe, and the means to alleviate misery. Today, one has to be something of an optimist to have an other than apocalyptic view about the way in which scientific and technical power will be used by (some) humans. Perhaps the most important probative thesis is that the most evil behavior is, for most individuals, learned, not instinctive. At least, that our brains have enough plasticity to enable a good society. So evolutionary psychology (and I am highly skeptical about its more deterministic versions) becomes the centerpiece of our scientific enquiry. My working hypothesis is that warfare was the central driver of natural selection for the enlargement and elaboration of the human brain. However, it is an extraordinarily plastic organ, and it may be to culture that we owe all the detailed specifications of its performance, in language, music, logical reasoning, esthetics, social integration. That brain is therefore not necessarily committed to the tribal warfare that engendered it. But we have until now totally lacked the tools by which to test these propositions — they have been purely speculative. I trust that we will learn in time.



Arthur Kornberg, 1999 (photograph by Magdolna Hargittai).

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Arthur Kornberg

Arthur Kornberg (b. 1918) is Professor Emeritus (Active) at the Department of Biochemistry of Stanford University School of Medicine in Stanford, California. He shared the Nobel Prize in Physiology or Medicine for 1959 with Severo Ochoa "for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid." Arthur Kornberg got his B.S. degree in 1937 from the City College of New York and his MD in 1941 from the University of Rochester. He served in the United States Public Health Service from 1942 till 1953 at the National Institutes of Health, and in brief leaves at New York University College of Medicine, Washington University School of Medicine in St. Louis, Missouri and at the University of California at Berkeley. From 1953–1959, he was Professor and Head of Microbiology in the Washington University School of Medicine and from 1959 he has been at Stanford University, in 1959–1969 as Founder and Chairman of the Department of Biochemistry. Dr. Kornberg is a Member of the National Academy of Sciences and a Foreign Member of the Royal Society (London). He has received the National Medal of Science (1979), the Gairdner Foundation Award (1995), and has many other distinctions. Dr. Kornberg has been very much involved in biotechnology companies. We recorded our conversation in Dr. Kornberg's office in the Beckman Center at Stanford University on May 12, 1999.

You are going to Rochester tomorrow to receive another honor. For you, going to Rochester to be recognized must have some special significance given your experience of discrimination while you were a student at

Microbiology Department, Washington University School of Medicine, St. Louis, 1957. Five people moved to Stanford in 1959 to establish the Biochemistry Department. They and R. L. Baldwin, who came from the University of Wisconsin in 1959, were the founders of the Department. They have stayed together and celebrated the 40th anniversary of the Department in 1999 (courtesy of Arthur Kornberg).

the University of Rochester, as you described it in your book, For the Love of Enzymes.

Yes and no. I do have mixed feelings. Anti-Semitism is an issue that has to be confronted. Even though my children and my students don't understand it and can hardly believe it, it happened to me and it wasn't a trivial encounter. Anti-Semitism was pervasive in these United States, including academia. I have called it a virus that has been endemic for two thousand years. It isn't going to go away and on some occasion, in some context, it will come up again. When the Premier of Malaysia recently blamed their economic meltdown on the Jews, we become aware that it can surface in many places. Fortunately, in the post-World War II period, things did turn around and there were many reasons for it. The University of Rochester medical school, as many other institutions, had small and tight quotas for Jewish students. I was one of two in my medical school class. That institution now has its President Tom Jackson, who is married to a Jewess, Jay Stein who is responsible for all medical affairs, and Lowell Goldsmith who is the Dean of Medical School.

Arthur Kornberg with the book *For the Love of Enzymes*, 1989 (courtesy of Arthur Kornberg).

In my time, the Dean of the Medical School, George Whipple, was the god of that universe. He bestowed upon two students a fellowship year in pathology, at the conclusion of which those students were on a greased track toward an academic career. I was not offered that fellowship, even though I later learned that I was the top student in that class. An instructor at Rochester at that time and later a professor at UCLA, Sidney Madden, said on the occasion of a discussion of grading students: "Arthur, I am so surprised that you were so critical of what the Dean practiced in grading students, namely, his personal evaluation of the quality of the student." I said, "Sid, that's precisely what I'm not going to do. My evaluation is going to be utterly objective." And he said, "Why?" I said, "Look, let's not beat around the bush, Whipple was anti-Semitic and it figured in his judgments." To which he said, "You know, you're right, but he didn't like Italians either." (This exchange took place on the occasion of a meeting of professors of microbiology and pathology on how to evaluate student performance.)

I would like to complete the story with an ironic twist. Two years ago Jay Stein and others conceived of a major new research building because Rochester was slipping badly in its scientific status. Jackson, Stein, and the Trustees decided to reverse the trend. They invited me to give some lectures, which they hoped would energize their effort. They told me they had a problem because the largest auditorium they had was the Whipple auditorium, and they knew how I felt about him. Of course, I agreed to lecture in that

auditorium. The irony is that now the Whipple auditorium has been replaced by a new one in the Arthur Kornberg Medical Research Building.

This story gives you a sense of why I am involved in this Rochester effort because the leadership of that institution is trying to do something significant in medical science. Apropos, in the early 1960s, the President of the University of Rochester, Allan Wallis called on me here at Stanford to ask if I'd be interested in becoming Dean of the Medical School. I said, "Not really. My interest in administration stops at being the chairman of a small department." Then he asked me, "Wouldn't you have some sentimental reason for coming back to Rochester?" "No," I said and I explained to him why. He then said that at that very time he was at Stanford and the prejudice was just as bad. This gives you the flavor of how things were. My students and my children can't imagine it. I wonder how these otherwise decent and humane professors, some of whom I liked and admired accepted this kind of treatment of me and others? The answer for some might have been to spare me rejection at the next level. It was the system people felt helpless to cope with, except one professor, Professor of Medicine, William S. McCann. He was the only one who had appointed a Jewish resident and who had singled me out to be helped in many ways. There were such brave people. Incidentally, at that time, the "America First" movement sought to avoid U.S. involvement in the European conflict both before and after Britain entered the war. McCann was the only member of the faculty I can remember who campaigned for "Bundles for Britain" in direct opposition to Whipple and others who were of the "America First," Charles Lindbergh mentality.

What did it mean, "being spared rejection at the next level?"

It is similar to the bias against women. Highly selected women, graduate students, often dropped out at the next barrier of marriage and domestic responsibilities and ceased doing serious science, hence the discrimination. In my case, my professors judged that it would be practical to train someone who would qualify socially as well as scientifically at the next level. I want to emphasize that these were not viscerally hateful people; in later years they were as kind to me as could be. In any community there are very few heroes, very few who have the guts and who are willing to be different. We have witnessed McCarthyism and other such movements even in our wonderful country. In any case, it's an issue as you know that people would rather not talk about and try to avoid. But we are getting very much off our main subject.

What turned you to science originally? You majored in chemistry. What turned you to chemistry?

No person or incident that I can recall. I was a good and avid student but I was not the penetrating and thoughtful student, as Darwin was a naturalist. When I took chemistry it interested me much like everything else did. I got good grades in chemistry. Why did I major in science when I went to City College rather than social science or humanities? I really don't know. In high school I had good and supportive teachers in biology and in chemistry and I was only 15 when I entered college. My life was pretty much governed by economic problems. My family was very poor. I worked every evening and weekends. Nobody in my family collected anything. There was no knowledge of science. There weren't any physicians in my family. My background was entirely lacking in anything that related to science, even medicine. But my parents endured sacrifices for me to go to college. I did well in my courses and at one point the Dean of Students, Morton Gottschall, a very kindly person, called me in to ask what I was going to major in. I said, "Chemistry," and he said, "Not really." There were no jobs available in chemistry. I wouldn't be employed in any chemical company because of being Jewish. When I suggested that, perhaps, I could teach in college, he discouraged me from chemistry as a career and urged that I consider medicine, since I was also interested in biology. There again, if I had looked at it closely I would've been just as discouraged. Medical schools were largely closed to Jews. Even Columbia University down the street hadn't filled a scholarship available to a City College student for the previous nine years, and not for the lack of good applicants. Going to medical school was a means of avoiding employment in Macy's, or being a high school teacher, neither of which inspired me. Medical school was a way out, I could spend four more years being a student. Also, medicine was regarded as a fine profession in my social circle. Fortunately, Rochester chose me; I really don't know why.

How did you choose Rochester?

I had something of a wanderlust. I probably could've gone to a medical school in New York but I always chose to go to places distant from where I lived, in grade school, high school, and then in college. I chose the distant City College over the closer Brooklyn College. City College was unique then. Requirements for admission, based on grades, were very high. Brooklyn College was only a half-hour from where I lived instead of an

hour and half on the subway to City College. City College was almost all Jewish, highly competitive and demanding. There were some great professors although there was no mention of research, and no opportunities and no encouragement to do research. I had no idea of what research meant. Professors engaged in any research had to do it somewhere else by moonlighting. I studied the textbooks and did the lab assignments. I was unaware of current advances in chemistry let alone what had been done 10 or 20 years earlier.

I finished college at 19 years in the depth of depression, and went on to medical school. Rochester at that time was an excellent medical school. There were many opportunities to do research, but none was offered to me. Eventually, I became interested or even obsessed with collecting data. As a medical student I contracted all diseases in the pathology textbook; recovery from one replaced another. I had mild jaundice and collected data. From blood drawn from other medical students, as well as my own, I learned that about one out of 20 of us had my kind of elevated bilirubin level. With a gift of $100 from my devoted professor, William S. McCann, I could buy bilirubin from the Eastman Kodak Co. I injected bilirubin into medical students and other "volunteers," and determined the rate of its removal from the blood stream. I had access to a corner of a bench at night provided by a kindly research associate. Those data were the subject of my very first paper. While most of my friends were medical students, I also had a few friends among graduate students, particularly the late Arnold Wolf in physiology. He was very helpful in showing me how to plot data in log-log plots to straighten out curves. I had no other tutor. I do recall Arnold telling me once that I was different from other medical students with some passion to do and understand something better.

I have just finished a great biography of Charles Darwin, by Jeanette Brown. I read and finish very few books but I finished that one. At one point I had the arrogance to make a comparison between us. Darwin was everything that I wasn't. He grew up in a wealthy, cultured family where science and evolution were freely discussed and his curiosity and collecting of invertebrates were encouraged. In his voyage on the "Beagle" he was again surrounded by people with intellectual curiosity. It was the Enlightenment Period. Yet he was not a very good student, but still a devoted naturalist. In each of his stages of development in intellectual surroundings, he felt driven to do something exceptionally well. That did not characterize my upbringing at all. I was led by circumstances. When I finished medical school I planned to be a physician. I entertained no alternative. I pictured

my career to be like that of some professors of medicine who wore white lab coats a few hours a week. They were my image of the scientist physician, but they were really amateurs in research.

Did you have any heroes, then and later?

Over the years, there were a few of my age and senior to me whose work and personality I very much admired.

Before pursuing aspects of my research career, you should know that in 1942, after completing my internship in internal medicine, I was assigned to the Navy as a ship's doctor. Then I was reassigned from sea duty to the NIH largely on circumstances that had to do with that trivial paper of mine on jaundice. Let me elaborate a bit. The yellow fever vaccine being given to troops going to the Pacific was loaded with hepatitis virus. Tens of thousands came down with hepatitis. Since there had been no literature on anything related to jaundice for many years, my paper was identified because it had the word jaundice in the title. That helped me get to the NIH where I was assigned to a group working on rat nutrition. It was an uninspired kind of research but I found it consuming. Within a year after being launched into a medical career, I found it more fulfilling to work with rats than people because I could control the experiments. None of my classmates who went to the NIH made such an abrupt decision. I'm pleased that then and later, on several occasions in my life, I made prompt decisions that may have seemed impulsive or even irrational to my friends.

After three years of feeding rats, counting the live and dead ones and keeping track of their weights, I began to find the work uninspiring compared to the new biochemistry, which I was hearing about but had never been taught: ATP, bioenergetics, muscle contraction, enzymes that did things beyond pepsin and trypsin, were all utterly new to me. I heard a seminar at the NIH given by Edward Tatum who later shared part of the Nobel Prize with George Beadle for their one gene — one enzyme hypothesis. I had hardly heard of genes. Genetics wasn't then considered in medical practice, or even in biology, strange at it may seem. This simple seminar was based on *Neurospora*, an organism I'd never heard of. I was fascinated by the seminar but my senior adviser told me that it was of no importance. But I did have three colleagues with whom I could share my excitement. There were four of us: Leon Heppel, Bernard Horecker, Herb Tabor, and myself. We met every noon for lunch and reviewed the current literature very seriously; we taught ourselves modern biochemistry. We read and

examined the *Journal of Biological Chemistry* from cover to cover. We were close friends and mutually supportive.

When the war was over and I felt liberated from feeding rats, I prevailed on my Research Director and the Director of the NIH to let me go off to learn about enzymes. The vitamins were near exhausted by then and enzymes seemed to be the coming thing.

So I was given permission to work with Severo Ochoa. Others helped me identify him. Ochoa was a Spanish refugee who then had little reputation. But he was a very serious scientist. He had no overt political leanings, but his family and friends were all Republicans. He had gone to Germany to do biochemistry and when Germany was no longer hospitable he went to England. With the onset of World War II, he found a place, in 1942, in St. Louis, in the laboratory of Carl Cori. There were few laboratories in the United States that were hospitable to Jews and refugees: Carl Cori in St. Louis, Hans Clark at Columbia, and perhaps some others. Carl Cori, one of my heroes, made a place for Ochoa, Herman Kalckar, Luis Leloir, and many others. Ochoa then moved on to be a guest at New York University in the Biochemistry Department. He was generous in taking me on when I didn't know ATP from ADP and knew nothing about enzymes. He gave me my start and opened up a new world. In nutritional studies you feed rats for two or three months and then you forget why you had started the experiment in the first place. I was electrified by what I could do with spectrophotometry, completing an enzyme assay in two minutes.

Ochoa had a remarkable imperturbability. Having been knocked around by political upheavals in Spain, Germany, and England, by now in his forties without a laboratory of his own, he still had an air of detachment and complete devotion to science. He enjoyed music, good fellowship, and fine dining. Being with and working with him day in and day out I felt that I might some day be able to do what he was doing. I was in much greater awe of Carl Cori.

Cori was a man of great intellect with a prodigious command of physiology and medicine, an aptitude for chemical kinetics and chemistry. I didn't know that I'd ever match Cori in his intellectual breadth and capacity, and, maybe, I haven't. Cori was a Czech from Prague and so was his wife Gerty. She came from a Jewish family but in all the time I was with her, this topic never came up. I understood the trauma of anti-Semitism that forced both of them to leave Europe in 1920–21; Carl was concerned that she would never have any academic advancement in those turbulent times in Europe. Gerty liked me and helped me. She was a most remarkable

scientist and woman but died in 1957, at the age of 61 of anemia. In the later years Cori mellowed a lot and we grew much closer.

Among my heroes, I want to mention H. A. Barker at Berkeley, who was trained as a chemist but became a microbiologist. In 1951, I spent the summer in Berkeley in his lab and later, in 1952, he took a sabbatical in my lab at the NIH. I have the greatest affection and admiration for him and his science.

You quoted the late Lars Ernster, in your book For the Love of Enzymes, *who estimated that 40 percent of the chemistry Nobel Prizes as well as 40 percent of the Nobel Prizes in Physiology or Medicine have been in biochemistry.*

This would not happen in the U.S. Lars and others on the Nobel Committee got nasty letters from professors at Stanford and elsewhere. They said, "Leloir? We never heard of him. Peter Mitchell? We never heard of him." Because they hadn't heard of them meant to them that Leloir and Mitchell didn't do chemistry.

You quoted Otto Warburg in your book, saying, "Where structure begins, biochemistry ends." I'm puzzled by this quote.

He was not speaking of the structure of ATP or a small molecule. He meant large structures that were cellular or sub-cellular. How can one do biochemistry on a nucleus? These were biological entities that could not be analyzed by conventional biochemical approaches.

Then you've said, "Spotlight moves so quickly [in biochemistry]."

Sure, does.

Doesn't it elsewhere too?

I am aware of it in biochemistry because I can identify myself with people around me over the last 50 years and see where areas and people have been caught briefly in the spotlight and then never seen again.

You have remained in the spotlight for a long time.

I was lucky. It so happened I worked in a field that was glamorous and has remained so. The impact of DNA and its transactions have remained in the center of attention. I did some of the original biochemistry on

replication and I continued to be active in that field for many years. But I left it a few years ago to start something new. To jump ahead, I am now consumed with another polymer, inorganic polyphosphate.

One final quotation from your book, "The hour lost can never be recovered."

People tell stories about me. I've had well over a hundred students who in turn had students. Stories circulate that are largely embroidered or fictitious. One that has been told and is in essence correct is about my obsession with time. I'm very conscious of the passage of time and certainly with the loss of time. That goes way back to when I was a teenager.

Once when my technician told me that he'd lost a sample in the centrifuge but fortunately still had some of that sample and could do that experiment over again, I might have said: "But you did lose much of an afternoon with that accident."

I also remember meeting two senior scientists, both accomplished biochemists, and discussing a procedure that they had suggested. I said, "I tried that and I wasted a whole afternoon on it." One turned to the other, mockingly, "He wasted a WHOLE afternoon on that procedure." But it's true to this day. My clock is always in front of me. I may pick up an issue of *Nature* and tell myself: "I must not spend more than ten minutes reading this issue." Then I'm upset because there are so many things to read that are interesting and diverting. Yes, time has always mattered. When you get to be an octogenarian, the passage of all those decades do matter.

Being an octogenarian is a relatively new experience for you.

I am 81 but I'd been anticipating it. Fortunately, I still want to be engaged and competitive with a concern that I'm taking up space and occupying the attention of eight young people. I don't want to let them or myself down.

Some hold the opinion that you need not learn much of what had happened in your field when you start your research, just find out what is at the frontier and proceed from that point and make the discovery.

It does annoy and disappoint me that my students have never heard of the people, heroes of mine — Carl Cori, Severo Ochoa, Harland Wood, H. A. Barker, Fritz Lipmann — they don't even recognize the names, let alone what they did. In their defense, they're bombarded and deluged

with information. The amount of reliable, sophisticated data from many sources cannot be assimilated by anybody. To ask someone to go back and read accounts of people who don't figure in present-day events, is certainly not part of a diet that a current student can consume. Yet children still keep learning the names of all the American Presidents, most nonentities, and British children learn the names of Kings. A legitimate concern is that classical biochemistry is being eclipsed and abandoned; students are not entering biochemistry graduate programs. Biochemistry as such seems passé, compared to the frontiers of neurobiology, developmental biology, and cancer biology. Biochemistry has been incorporated in most fields of biology and medicine. A dozen departments in a medical school and in the biological sciences, are in essence departments of biochemistry. Chemistry is the universal language that expresses what all of these previously diverse disciplines are about. I find that inspiring. When you pick up any journal in the biosciences, it is either chemistry or has chemical insights.

You have stressed that your DNA work did not originate from the Watson-Crick discovery of the double helix.

That's true. I'm neither proud nor ashamed of that. My first interest in DNA was not the basic processes of replication and heredity. I'm not proud of that. The Watson-Crick model provided a scheme for how genetic material could be used for transcription and replication. I was aware of that epochal paper in 1953, but was not transformed by it. Nor did it put me on a track to find the enzyme that replicates DNA. Some years earlier I had gone on from studying enzymes that made a coenzyme, a dinucleotide with a pyrophosphate bond. I was inspired by the work of the Coris who had first found the enzyme that made glycogen, a polysaccharide. Could I do the same with a DNA chain? I had acquired the technology to label each part of what might be the building blocks of DNA. For several years I worked on how the cell makes a pyrimidine nucleotide and phosphoribosyl pyrophosphate (PRPP), a precursor of nucleotides. I developed a sense of what a nucleotide building block might be, namely a deoxynucleoside 5-triphosphate. My initial hope was to extend the chain of something as complicated as DNA. Then I was lucky, fabulously lucky, because I found and could sort out the many enzymes — actually seven new enzymes in addition to DNA polymerase that were needed to extend a DNA chain. We discovered the four deoxynucleoside triphosphates. I entitled a recent lecture in Israel "The Ten Commandments of Replication Enzymology." I described the many steps we took to get to DNA polymerase, an enzyme

unique in enzymology because it took instructions from its substrate, the DNA template. Many people found it hard to believe that an enzyme could do that.

When we pursued this enzyme and found that it needed a template, it was obvious immediately that this fit the Watson-Crick model of how the double helix of DNA was replicated. Although I was not immediately inspired by the model, a year later I was keenly aware of its implications as we pursued the properties of the enzyme that replicated DNA.

Your book gives me the impression that you're giving a great emphasis to Gobind Khorana's contribution to deciphering the genetic code by his syntheses of fragments of DNA while Marshall Nirenberg's contribution is not mentioned.

I should have included Nirenberg. His discovery that poly(U) could be translated into a polypeptide was a breakthrough in deciphering the genetic code. My emphasis on Gobind Khorana's contribution was based on the totality of his work over many years. Khorana as a classic organic chemist did something utterly novel in using enzymes in his syntheses to solve important biological questions.

Now I would like to turn to your research. You received your Nobel Prize in 1959 and your first paper on enzymatic synthesis of DNA was rejected by the Journal of Biological Chemistry.

The editors did not reject it outright. They didn't want me to call the DNA polymerase product DNA. They wanted me to call it a poly-deoxyribonucleotide. There were many reviewers and a lot of controversy. But I wouldn't change the title of the paper. There was a lot of other minor criticism. Does the name Chargaff mean anything to you?

I'm a great admirer of Erwin Chargaff.

I'm not. I can admire his literary gifts and his contributions to DNA chemistry. He is a complicated man. In his brief autobiography in the *Annual Reviews of Biochemistry* he mentions that he was out of step at ten.

He was very self-critical too.

And very critical of me. He was prominent among the editors who wanted my papers rejected. Chargaff in the 1940s, applied paper chromatography

to digests of DNA. He made the remarkable discovery of an equivalence of A to T and of G to C in all DNAs. What's more, he found that the ratio of A plus T to G plus C was characteristic of a species. In 1956, three years after the Watson-Crick paper, at a symposium on the "Chemical Basis of Heredity" at Johns Hopkins in Baltimore, there was a great excitement and acceptance of the Watson-Crick model proposed three years earlier. Crick's paper and mine too emphasized base pairing of A to T and of G to C in the replication of DNA. Chargaff's paper ridiculed base-pairing and rejected it as a source of polypeptide information. Not only did he not discover base-pairing, he rejected the model after it was well accepted. To be sure, his discovery of the base equivalencies helped the model as did the unique ratios of A + T/G + C help validate DNA as the genetic substance.

Chargaff was dismissive of molecular biology and used his formidable literary skills to make his point. As for my DNA replication papers, John Edsall, when he became Editor of the *Journal of Biological Chemistry* in May 1958, promptly accepted them.

Would you care to say something about your wife, Sylvy, who was a wife, a mother, a scientist.

Sylvy was a fine scientist and beloved by all. I've had two major tragedies in my life and her loss was the greatest. When we were dating, I mentioned that I'd gotten a perfect grade in chemistry in the New York State Regents' Exam. She said, "I did too," and then asked me, "What did you get in

Sylvy Kornberg (née Levy) and Arthur Kornberg on the occasion of the announcement of Arthur Kornberg's Nobel Prize in 1959 (photograph by Barney Peterson, courtesy of Arthur Kornberg).

algebra and geometry?" I got 97 but she'd gotten 100 in each of them. But she never had the hubris of her great intellect.

Was she much disadvantaged as a scientist by being a wife and mother of three children?

I suppose so. She liked to do science and she did it well but unlike Gerty Cori, was not intensely ambitious. Her devotion to me and our young children made it very difficult to maintain the pace in science. She was happy to help, guide, and admire our wonderful children.

You had, obviously, an impact on their careers.

Hard to tell. My eldest son Roger, now a distinguished scientist, was fascinated with science from an early age. When we asked him at nine, "What do you want for Christmas, Roger?" His response: "A week in the lab."

My second son Tom never entered the lab and studied the cello full time. He attended Juilliard and was a student of Leonard Rose. His classmates and still close friends include Yoyo Ma and Emmanuel Ax. Tragically, Tom developed neuromas on his left index finger and had to give up playing. While at Juilliard he was also a full-time student at Columbia College. He took chemistry, physics, and biology. While there in 1969–1970, John Cairns found a mutant of *E. coli* that appeared to lack DNA polymerase but could still make DNA. My work came into question in the minds of many people. How could replication go on in the absence of this enzyme. *Nature* magazine led a chorus that DNA polymerase was a "red herring." Tom proved to be a gifted experimentalist. Within a few months he discovered novel DNA polymerases. The one that I'd discovered first had a role in replication but it was largely involved in repair of DNA. All three DNA polymerases have the same mechanism but are used for different things in a growing cell. After these electrifying discoveries after only a few months in the laboratory, Tom went on to graduate school and later to postdoctoral work in molecular genetics. He is now Professor at the University of California in San Francisco, doing very important work in developmental biology.

My third son Ken is an architect. But at Stanford he took physics, biology, chemistry as well as architecture and mechanical engineering. Now he is the most gifted designer of laboratories and very much sought after. He has a profound understanding of the science that his brothers and I do and a flair for design.

Arthur Kornberg in 1971 (photograph by Y. Karsh, courtesy of Arthur Kornberg).

Did I influence them? My wife and I influenced them by our love for and devotion to science. Naturally, you influence your children in many ways. But I never discouraged Tom from being a cellist. I admired and applauded his career in music. I've been equally supportive of Ken as an engineer and architect. I have a profound admiration for what they're doing. From the very earliest age when they were still in diapers, I would take them on trips with me. Later on there were more extensive trips, week-long trips when I was visiting professor somewhere. Even though I was busy and consumed by my preoccupation with time, my sons will tell you that I always had time to be with them. These trips were great, for them and me. With three boys, so close in age and highly competitive, it was good to take one to be the center of my and other peoples' attention. Now they're very close friends, devoted to each other. There's nothing more that a parent can wish for. Tragically, my second wife, Charlene, died of leukemia, a great, great shock, four years ago. I recently married Carolyn, someone I knew for many years, a friend of the family, an astonishingly wonderful person. She has no family of her own except for an aged mother. She has adopted my family and they are attached to her. There have been some very difficult times but it's in my nature to look ahead and not to dwell on what might have been.

You didn't seem to be too generous with Kary Mullis in your book The Golden Helix: Inside Biotech Ventures.

He epitomizes what I find wrong with celebrity in science and the Nobel Prize. Kary Mullis never did anything important in science and he never will. He hit upon an idea, which may have seemed original to him,

but Gobind Khorana and his group had already carried amplification of DNA many years earlier. The polymerase chain reaction (PCR), which was made practical by Mullis and the staff at Cetus, was a tremendous technical advance. Yet it would have been made more than ten years earlier had the techniques of nucleotide sequencing and oligonucleotide synthesis been available. The concept of extending a primer and copying a template were well known from my work twenty years before. The fact that DNA chains come readily apart and re-anneal was also very well known. Mullis was able to exploit these properties in 1985, when the new technologies became available. Khorana couldn't exploit them in 1969 because DNA sequencing and automated nucleotide synthesis were not available. Kary Mullis flaunts a frivolous disdain of science that means so much to me.

Do you agree that he deserved the Nobel Prize?

No. It was a mistake. Yet Alfred Nobel wished that the Prize be awarded for a discovery rather than for a lifetime of achievements in science. It may be one of the attractions of the Prize that someone can get very lucky and win the Prize as in a lottery.

Isn't it we who overreact to the Nobel Prize?

Absolutely. Yet, there is a certain charm that any one can say, "If this crazy experiment works, it can win a Nobel Prize."

I had planned this question for you, "Scientist in the Courtroom." Is it possible to do in a courtroom what appears impossible otherwise in educating the public to science?

My respect for science is unqualified. One of the greatest advances in civilization is the discipline of science. But scientists are still people. I have seen instances in the courtroom when scientists have not told the whole truth. You would've hoped that the discipline of science would've made them more disciplined in the courtroom too.

Isn't your field even more vulnerable than most because of the direct outlet into biotechnology, because of the possibility of almost instant fame and wealth?

Until rather recently, biologists, unlike chemists, rarely found employment in industry. We considered it a tragic outcome when one of our students

entered industry. None of us ever expected biologists and biochemists to become so entrepreneurial. Some of us saw opportunities for technology that could not be done in an academic laboratory. We could see technologies with an impact on medicine or agriculture. Of course, there are temptations to make money and become financially independent. None of us ever thought of patents. Now there's an Office of Technology and Licensing at Stanford with more than 20 people. I now feel irresponsible if I don't inform them of something that may be patentable. The whole climate has changed. It's not all bad. There are pros and cons of commercial partnerships with academia. Yet universities and their boards of trustees are often deluded by the apparent innocence of such involvements. Partnerships with profit-driven industry can have negative features that overweigh the positive.

Regarding patents, I want to focus on the prominent efforts at several levels in academia to exploit intellectual property by patent licenses and royalties for support of basic research. This may be a serious delusion. As one of several examples, let's examine in detail the Cohen-Boyer patent for recombinant DNA in plasmids. This patent has been many times more lucrative than any other biotech patent in academia.

To begin with, this patent should never have been granted. But because of the modest $10,000 license fee, it was never contested. The patent was shared equally between UCSF and Stanford. Over its near 20-year life from 1980–1998, license fees netted $97 million for Stanford, allocated one-third to Stan Cohen, the inventor, one-third to his department, Genetics, and one-third to the Medical School. There is no accounting of how this money was used. Let's be generous and assume that half — about $50 million was devoted to basic research, about $2.5 million a year.

Now let's compare this number with the near $250 million a year that the Medical School gets from NIH, NSF, and other government sources to pursue basic research and training. Obviously, the annual income from this most lucrative of all biotech patents was only about 1 percent of what was provided by the federal government.

Despite these concerns, I want to emphasize that I regard to be the positive features of academic scientists and engineers participating as consultants and even as partners in biotech ventures. They bring expertise, they are a conduit for application of the vast knowledge generated in academia, and they elevate the quality of science and engineering in the industry. The growing industry in turn provides more jobs to employ academic graduates. Another powerful gain from academic-industrial relationships is the accelerated pace with which the technology generated in industry is applied to basic research.

You visited the Soviet Union in 1959. It would be interesting to hear what you have to say about this visit from a perspective of forty years.

I was a member of an official National Academy of Sciences delegation. There were five: Konrad Bloch, Herbert Carter, Bernard Davis, Albert Lehninger, and myself. DNA and genetics was under the tight grip of Lysenko but the students and the scientists we talked to knew better. It was refreshing to them to hear about DNA replication, genetics, the one gene-one enzyme development. We were very well received. Our hosts were warm and cordial.

I think we made an impact. At the conclusion of our visit we met with high officials who wanted to know our impressions. We tried to find attractive things to say but they persisted: "Be frank. Tell us exactly what you think of how we manage our science?" We described how we reorganized the support of science in the past ten years, in which the NIH gave grants directly to an individual, young or old, to someone unbeholden to a Professor, Dean, President of the university and local bureaucracy. We described how each scientist became an entrepreneur whose achievement could be monitored and whose support could be extended or terminated. Direction of science was from the bottom up, rather than the top down. One high official said, "What you're doing is strange. It's different from standard practice here and elsewhere in Europe." Forty years later, to this very day our support of science is relatively unique in the world. When I go to Japan, which I do quite often, I end up saying: "No matter what you call it, it's still research direction from the top down." This extraordinary development of research support in the U.S. deserves to be analyzed and chronicled in depth.

Could you, please, tell us about your recent interest in the inorganic polyphosphates?

I thought you'd never ask. I stopped almost abruptly working on DNA replication about eight years ago and switched my attention to this inorganic polymer. Let me go back a bit. When I entered biochemistry in 1946, mitochondria were known, but the mechanism of aerobic phosphorylation, how ATP was synthesized, was not. In 1947, when I was in Cori's lab, Jean-Marie Wiame from Brussels informed us that metachromatic granules observed in many cells (e.g., yeast, bacteria) were aggregates of inorganic polyphosphate. The phosphate residues were linked by anhydride bonds as in ATP. Later on, Albert Lehninger and Eugene Kennedy established

that the mitochondria fix phosphate on ADP to form ATP. Polyphosphate remained on my mind. How does this huge polymer get made? The ease of its synthesis by dehydration of phosphate made it likely that polyphosphate existed. Also, polyphosphate was known to be a phosphorylating agent, and could form peptide bonds. Now we find it in volcanic condensates and in deep sea steam vents. It could very well have been a catalyst and precursor in prebiotic times. Most remarkably, it is now found in every cell in nature: in all bacteria, fungi, plants, and animals. There is no cell in nature in which it hasn't been found. Poly P chains are generally hundreds to a thousand residues long. In 1955, my late wife, Sylvy was using extracts of *E. coli*, in connection with our DNA polymerase work. With ATP (^{32}P) labeled in the end (gamma) phosphate, some extracts produced ^{32}P-poly P. We then showed the reaction to be reversible: poly P converted ADP to ATP. Distracted by our DNA replication, we didn't do anything further with it. Over the ensuing years, others confirmed the ubiquity of poly P. Harland Wood, one of my heroes in biochemistry, showed that the *Propionic bacterium* (the organism that he had used to show CO_2 fixation), used poly P rather than ATP in phosphorylating glucose. With no known functions poly P was called a "molecular fossil."

In 1989, Kyunghe Ahn, a postdoctoral fellow, trained as an organic chemist, wanted to learn enzymology. I suggested that she purify the enzyme we found in 1955. She obtained the enzyme in a homogeneous state. We named it polyphosphate kinase (PPK). With reverse genetics, we later found the gene for PPK and knocked it out. We could also over-produce PPK. These genetic manipulations gave us clues to the function of poly P. With the pure enzyme, we had a reagent that, for the first time, was specific for poly P. The enzymes made ATP from poly P or could use poly P to make ATP. In the course of looking for the PPK gene we discovered another that encoded an exopolyphosphatase, which also proved to be a great reagent. These are novel methods that are specific and sensitive and are susceptible to high-throughput assays.

My approach to physiology is to isolate the actors (the enzymes) with which to investigate the dramas they perform. We were puzzled that the cells that lacked PPK and poly P grew well. Eventually we found that late in the life of a culture when it goes into a stationary phase, poly P was needed. For lack of poly P, many genes needed to resist stringencies and stresses are not turned on; the mutant cells die in a few days. Poly P acts as a regulatory molecule. Even in small amounts it is needed in the stationary phase of a culture. During the past year we learned that

the enzyme (PPK) is hugely conserved in more than 20 bacterial species, including many of the major pathogens. Among them, it is known that their virulence genes are turned on in stationary phase as in *E. coli*. Were we to knock out the PPK gene in the pathogens, would they remain virulent? We have the technology to do just that. For the past year, we've knocked out the genes in some of these pathogens, and now find in animal tests that poly P is essential for virulence. To do these animal tests, it's difficult to get people do what you're interested in, when they're busy doing what they're interested in. But now, many in the infectious disease field are becoming interested.

Pseudomonas aeruginosa is one of these pathogens that causes a fatal pneumonia in patients with cystic fibrosis. Unfortunately this organism can't be reached by antibiotics or by the immune system. We have found that the mutants lacking PPK and poly P are no longer motile, can't perform synchronized swimming, called swarming, and lack still other modes of moving, such as twitching. They cannot form the biofilms that cause intractable pneumonia. Most recently we have learned that our mutants are avirulent in mouse models of fatal infection. If PPK proves to be so essential for virulence, then it becomes a novel target for an antimicrobial drug.

I am pleased that our pursuit of poly P, an inorganic polymer that few ever heard about (and those who did didn't care about) is now likely to become of considerable importance in the pathogenesis of bacterial diseases and may even lead to novel and useful antimicrobial drugs. This unprogrammed practical consequence of basic research is the most important message we can convey to our fellow citizens as well as our fellow scientists. Another such example is the consequence of our extensive studies of the enzymatic pathways of the biosynthesis of nucleotides and their assembly into DNA. These studies provided the design for the great variety of chemotherapeutic drugs, which we use today because the pathways of DNA replication provided many targets that are now susceptible to drugs that are used in cancer, AIDS, herpes, and autoimmune diseases. The enzymes we discovered made recombinant DNA possible and that's what ignited the biotechnology revolution.

What I find so gratifying about science even at my advanced age, is that new things keep coming up. Take biofilms that I mentioned a moment ago. I'd never heard about biofilms. When I learned about them only a few months ago, I realized that all these years we've been studying bacteria in a limited way. Since Louis Pasteur and Robert Koch, we have been

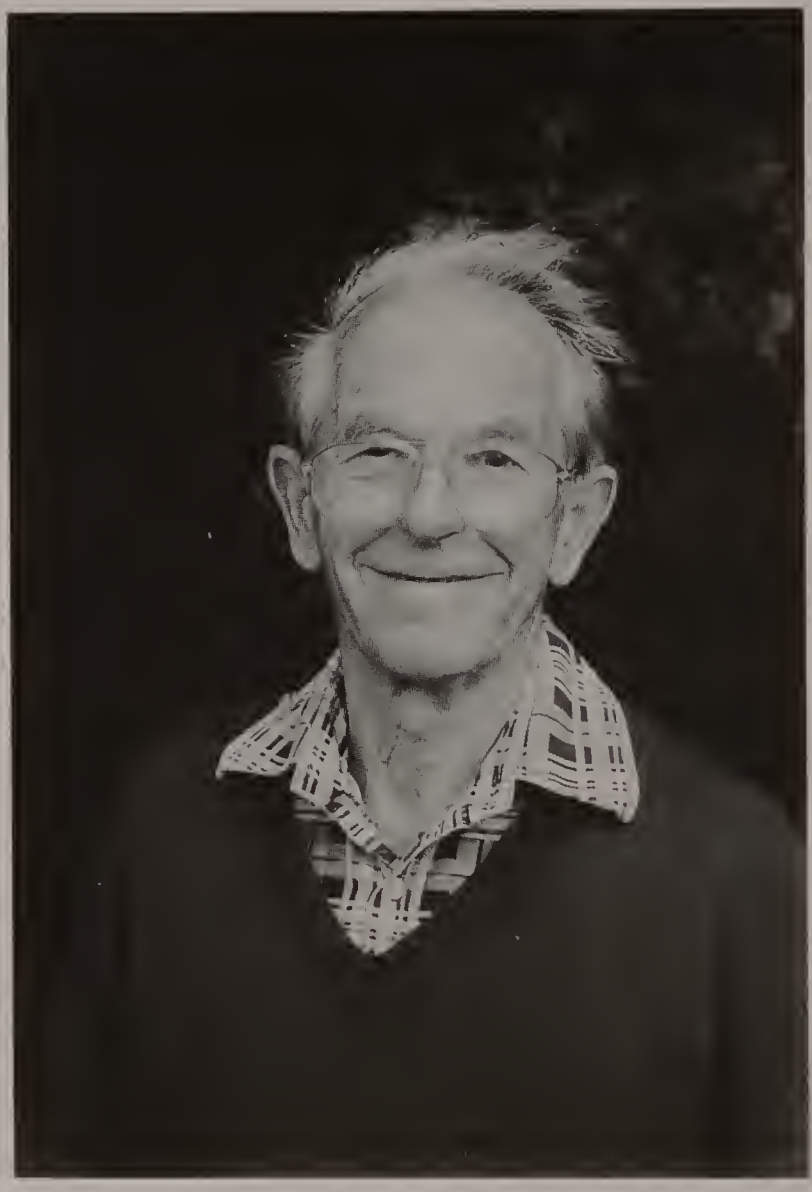
picking a colony of bacteria from a petri plate, putting it into a flask to grow in a rich nutrient broth. That's not how bacteria thrive in nature, whether in the mouth, called plaques, in the lungs, or on an implant. Of bacteria, pathogens and non-pathogens, 99.5 percent are disposed as biofilms. They're not unicellular; they are multi-cellular. They live in elaborate communities in which the bacterium, protected by a mucoid polysaccharide, is a thousand times more resistant to an antibiotic. There is only a beginning awareness of biofilms. Few scientists or physicians know about biofilms. Dental people have been aware of biofilms because of plaques and gum disease.

You make it sound a very interesting topic.

Biofilms and polyphosphate attract few people, unlike DNA, signal transduction, and cancer biology. It will take time before poly P and biofilms become noisy and crowded areas.

Would you like to add something to our conversation?

People have characterized my work as reductionist and anti-vitalistic. Current advances in genetics, such as transgenes in mice have an element of vitalism. You knock out a gene in a mouse, or you insert a gene in a mouse, and interesting things happen, but it's still a mouse. This is unlike studying an event *in vitro* where you can resolve and reconstitute it at the molecular level. I am in the minority who retain this reductionist conviction. Now with the power of reverse genetics, we identify the gene responsible for an enzyme, overexpress and knock it out. The power of the new technologies is to relate enzyme functions *in vitro* and *in vivo.* My reductionist, anti-vitalistic approach is to bring a biologic event into a manipulable *in vitro* system and resolve it into its molecular components. To this day no one has resolved and reconstructed a viral life cycle in molecular detail. It is a goal well worth striving for. When that is achieved, mysteries will be resolved and new vistas opened. My motto is: "If the cell can do it, we should be able to do it even better."



Frederick Sanger, 1997 (photograph by I. Hargittai).

5

Frederick Sanger

Frederick Sanger (b. 1918 in England) studied in Cambridge and received his B.A. degree in 1939 and his Ph.D. in 1943. He retired from the U.K. Medical Research Council Laboratory of Molecular Biology in 1983. Dr. Sanger is the only person who has ever received two Nobel Prizes in Chemistry. He received his first Nobel Prize in 1958 (unshared) "for his work on the structure of proteins, especially that of insulin." He then received a second Nobel Prize in 1980, jointly with Walter Gilbert of Harvard University, "for their contributions concerning the determination of base sequences in nucleic acids" (The other half of the 1980 chemistry Nobel Prize went to Paul Berg "for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA.") Dr. Sanger is Fellow of the Royal Society (London), Foreign Associate of the National Academy of Sciences of the United States, and a member of many other learned societies. His many awards include the Copley Medal and the Royal Medal of the Royal Society (London) and the Albert Lasker Basic Medical Research Award. Since 1981 he has been a Companion of Honor (U.K.; membership restricted to 65), and since 1986 he has been a Member of the Order of Merit (U.K., membership restricted to 24).

Our conversation was recorded on September 16, 1997, at Churchill College in Cambridge, U.K.*

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For starters, do you have any comment on cloning?

I don't think cloning has anything to do with my work. I have been concerned with sequencing, that is, determining the order of the amino acids in proteins, and later I changed to nucleic acids, and my most recent work was on DNA, developing techniques for sequencing that. Cloning is a different thing. I don't have any great opinion. The scare things, which the press puts out, are not very significant. It's not very likely that anyone would like to clone monsters. It's more just a social question, and if it's going to be of value to agriculture, then I think it's acceptable. It is something for society to decide, not for the individual scientist.

I read that you were always concerned about being useful. Your father was a medical doctor but you thought that a scientist could bring even more benefit to people.

Originally I was also expected to become a doctor. Before I came to college, I had to make a decision. It seemed to me that the life my father led was not really what I wanted to do. It was a very scrappy sort of a life. He was always going from one patient to another. I felt that I would be much more interested in and much better at something where I could get to really work on a problem. So I decided not to study medicine at the university. When I decided to study science, I didn't really have a clear idea of what I was going to do. It was fairly difficult to become a research worker; there was a lot of competition. If people had the opportunity to do research, they usually did. It was a rather prestigious thing and a very good life. I didn't really expect that I would become a research worker. I thought I would become a scientist of some sort and probably would get an industrial job.

Who else influenced you?

My brother was probably the first important influence on me. We were very close in age, just a year between us, and my early years were spent very much with him, playing in garden and so forth. He seemed considerably older than me then, and he was very much the leader and I was a quiet sort of fellow. I used to follow him around and I learned a lot from him. He was much more of an extrovert than I am. He got very interested in nature, and particularly in snakes. He was a great expert in finding birds' nests. My father was also interested in science and nature. He did

Frederick Sanger (in the middle) at the age of 11, with his sister and brother (courtesy of Frederick Sanger).

some work in immunology in Cambridge in what is now the Molteno Institute. He was identifying bloods by immunological techniques. He spent some time with Scotland Yard showing them how to identify human blood. He was an influence too. I grew up, as it were, in a scientific family. Eventually my brother became a farmer. We started being educated together. I did better at school than he did. He came to Cambridge University and studied agriculture and went into that field, being a more practical person than I am. There were, of course, many other people who influenced me later.

I heard that you declined getting knighted.

I just didn't feel it would suit me. It would somehow label you if you go around saying Sir Frederick Sanger, and I just didn't want that. It would put you in a separate class. It's just a personal thing.

I actually have the better qualification of the O.M. [Order of Merit]. That is specifically for something you've done. There are only 24 members, and I am fairly proud of that. Every five years you've a luncheon with the Queen. The last one took place in Windsor Castle and it was a splendid affair. It's an interesting occasion with so many well-known people in different fields. My wife likes that very much.

You were a conscientious objector in World War II. How did it happen?

I was brought up as a Quaker. Quakers don't believe in killing people and are very strict about that. My father was a very keen Quaker. He

joined when he was about 30. In addition, it was my personal feeling. Before the War, there was a lot of feeling against going to war. I signed the Peace Pledge Union, which was started by Dick Sheppard, who was a Church of England priest. I don't know what I would do now. I'm no longer a Quaker. When I started studying science, I found it very difficult to believe something that I did not know. In science you have to be so careful about truth. You are studying truth and have to prove everything. I found that it was difficult to believe all the things associated with religion. I call myself an agnostic. There are things that we can't explain, like our consciousness, and I have an open mind about that. Whether there is a God or not one can't tell. If you're a scientist and believe in truth, you've got to say you don't know when you don't know. Difficulties in science occur when people are not prepared to say they don't know. There's always a temptation, especially if you have a theory, to try to prove it rather than to find out what is the truth.

You're the only person who has ever won two Nobel Prizes in Chemistry. It is difficult to perceive that you had set out two great problems of tremendous importance and then solved them.

It was not quite like that. In fact, it all went by stages. I had got my Ph.D. with Albert Neuberger on protein metabolism. In that work I learned a lot about protein chemistry. I started off, by luck, working on proteins. I happened to get a job in 1943 with Professor A. C. Chibnall, who was the new Professor of Biochemistry in Cambridge. He suggested to me that I should try to look at the end groups of insulin, that is, at the amino acids at the end of a polypeptide chain. Chibnall was interested in the number of amino acids in proteins. Nothing was known at that time on sequencing. People had tried to do it but had not made much progress.

I think the reason for choosing insulin was that it was a protein, probably the only one that you could buy in a pure form. Chibnall had done a lot of analysis on insulin. There was this interesting fact that it had a lot of free amino groups in it. He put me on this problem of trying to identify these amino groups. I was successful in developing a general method for looking at free amino groups. It was called the DNP method (DNP = dinitrophenyl). You put a colored reagent on the free amino group at the end of the chain and then you hydrolyzed the protein and identified the nature of the DNP-amino acid. The DNP was linked to the amino acid by a stable bond. The peptide bonds in the chain were broken down by acid. In this

A. C. Chibnall, Professor of Biochemistry in Cambridge where Sanger started his work in 1943. Chibnall suggested to Sanger to look at the end groups of insulin (courtesy of the LMB Archives).

way you could identify the end groups. The main breakthrough that made this possible was due to previous work by A. J. P. Martin and R. L. M. Synge — the discovery of partition chromatography, which I applied to separating the DNP-amino acids. The work of Martin and Synge gave me the break. It was a very powerful fractionation technique. Previously crystallization and distillation were used for separating the amino acids.

So, you see, I didn't set out to solve the problem of sequencing. Rather, I just set out to determine the end group and worked out a general method to do it for proteins in general. I found there were two chains in insulin. One had phenylalanine at the end, and other had glycine at the end. One problem was that the DNP-glycine was rather unstable. When you did a complete hydrolysis, you didn't get a very good yield of the DNP-glycine, as it was broken down, so we had to cut down the time of hydrolysis. Then we found that we got a lot of other compounds produced. These turned out to be DNP-peptides. We looked at these and realized that we could get information about the sequence. With some work we could see two sequences of about four or five residues long. Those were the first

sequences determined in a protein. We had the two chains of insulin and we could separate the two chains. Our next achievement was to determine the complete sequence of the phenylalanine chain, 30 amino acids long, by breaking it up into small fragments, fractionating them, and looking at their structure. We were again helped by the work of Martin and his colleagues in a new development of partition chromatography. That was paper chromatography, which enabled us to fractionate amino acids or peptides on a sheet of paper in two dimensions. Eventually we were able to put the pieces together and determine the complete sequence. Martin and Synge were working at the time in Leeds, and Chibnall knew them well. Martin was the genius behind this. He discovered partition chromatography and went on to discover gas chromatography. He was a very inspiring person. I met him at meetings and he always had something new to talk about.

An important contributor to this work was a postdoctoral fellow, Hans Tuppy, who came from Austria after the War. He worked on the phenylalanine chain while I was working on the glycine chain. He was a very hard worker and finally got the sequence of the phenylalanine chain before we had finished the glycine chain. After that, he went back to Vienna and has become more interested in administration.

Frederick Sanger in his laboratory in the late 1950s (courtesy of Frederick Sanger).

When you received the Nobel Prize for the insulin work in 1958, you were 40 years old. Then you set out another big task in research. This is not very common.

A lot of Nobel prizewinners take on big administrative or teaching jobs or do something else. I am not very good at teaching and I don't think I would be very good in administration either. I don't think I would have enjoyed any of this the way I enjoyed research. I had this opportunity, having got a Nobel Prize, to have a steady job and good facilities. It was easy to get students, particularly postgraduate students, who were well trained and this helped very much with research. I was in a position to do more or less what I liked, and that was doing research.

Initially I continued to study proteins. In 1958, nothing was really known about sequencing nucleic acids. It didn't seem to be an easy problem for two reasons. One was that they were so big, and the other was that they had only four components. A sequence with only four components would be very much more difficult to work out than a sequence with 20 components. For a while I didn't see any hope of doing it, although I realized it was a very important problem. As DNA seemed quite impossible, I started thinking about RNA. The transfer RNAs were small, of about 70 or 80 nucleotides. It was around 1965 that I started working on RNA.

Celebrating Sanger's second Nobel Prize in the canteen of the LMB. In the middle, Frederick Sanger, Sydney Brenner, and Max Perutz (courtesy of the LMB Archives).

I used to go to the Gordon conferences in New England. There was always one on proteins and nucleic acids. I was bored by the nucleic acid talks and went largely for the proteins. Gradually, however, some of the nucleic acid talks rubbed off on me and I became interested in it.

The chief problem was to obtain a small piece of RNA to sequence. The main progress was made by Bob Holley and his colleagues. They were able to isolate a pure transfer RNA and to sequence it, using the method, which had been developed for proteins. So we were beaten to that one.

After that, we developed a two-dimensional method for fractionating small degradation products of RNA, which proved quite successful. It was a combination of ion-exchange chromatography and electrophoresis.

We used this technique to study an RNA with 120 nucleotides in it, and this my Ph.D. student George Brownlee managed to sequence. This was the largest system to that date, around 1965. We devised a few new techniques for sequencing the products, and this got us into the nucleic acid field.

Did you patent your discoveries?

No, never. I worked for the Medical Research Council and they didn't allow you to patent things. They would do it themselves if they felt it was significant. Most of my work was not patentable. The only thing that one should perhaps have patented is the DNA sequencing method, which we developed, but we didn't. We were developing methods but never knew which of them would really be the ones that would work. The actual DNA sequencing method, which finally has taken hold, is called the dideoxy method. It was just another idea and one gets lots of ideas and tries them out, but this one just happened to work.

Was there any serendipity in your work?

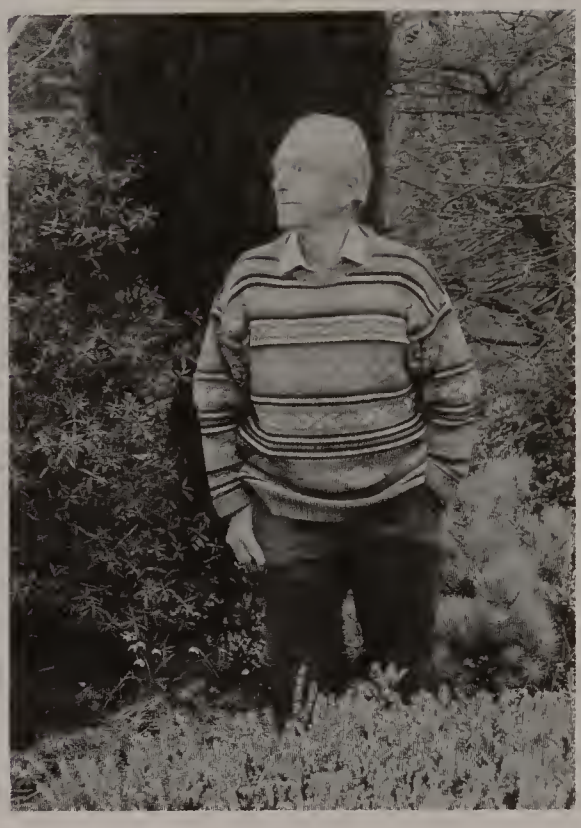
Quite a lot. The main luck was getting into the field, getting into protein sequencing when it was ready to be solved and getting into the nucleic acid sequencing when there was a chance of solving it. Most of our successes depended on recent successes of other workers.

What was your most important work?

I consider it was the dideoxy method, which was the climax of my work. That did make it possible to sequence large DNA molecules. With this method

you could work directly with the large molecule. The smallest DNA we could get was that of a bacteriophage, which contains about 5000 nucleotides. Even that was quite ambitious. First, we tried to use the already existing method of partial degradation and looking at the fragments and managed to get some sequencing out by that method. We then developed a new method, which depended not on degradation but on the use of DNA polymerase, the enzyme, which normally synthesizes DNA chains. The method as finally developed makes use of the dideoxynucleotide triphosphates, which are analogues of the normal substrates but lack a critical hydroxyl group. They are incorporated into the growing DNA chains but act as terminators to further extension, so that if a single dideoxy derivative is used, then all the chains made will end at that nucleotide. This effect could be exploited for sequence determination. The other important factor was a new and very efficient fractionation system, which separated nucleotide chains exactly according to size; this was polyacrylamide gel electrophoresis. With these new techniques we were able to develop a rapid and simple method of sequencing DNA fragments of almost any size.

Frederick Sanger on an excursion in California (courtesy of the LMB Archives).



Frederick Sanger in his garden, 2000 (photograph of Magdolna Hargittai).

Did you continue working after the second Nobel Prize?

Till 1983. I retired when I was 65 in 1983. That's the standard retiring age in this country. I felt that I could achieve very little more. I felt also that I was getting old and my memory wasn't too good. For research, you really need a very good memory. I noticed that sometimes I would ask a student some questions and a week later I would be asking the same questions again. I also felt that there were many other things that I wanted to do and this would be a good opportunity to do the other things, which I hadn't been able to do. I had been working very hard all my life. I gave up the lab, and I really haven't done any research since 1983. The main thing I do nowadays is gardening. I bought a rather large garden. It keeps me busy.

You write very nicely about your wife.

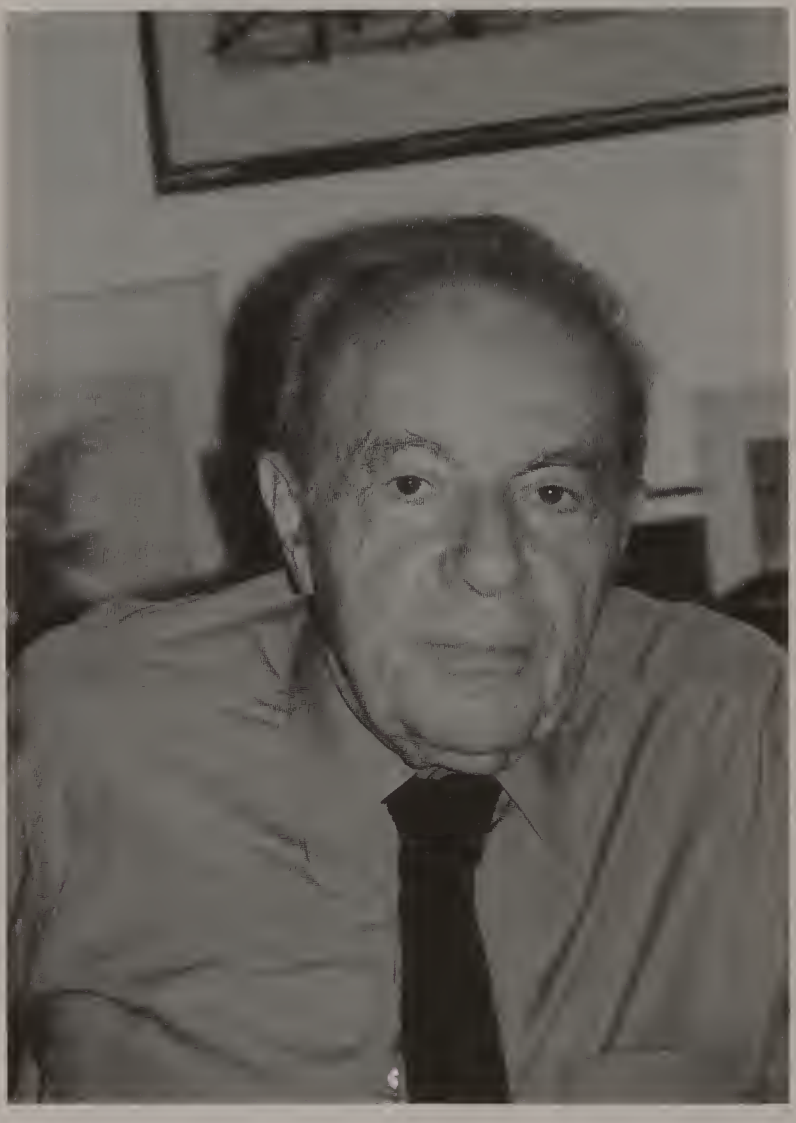
I met her while I was a student in Cambridge. She was also a student, studying economics. She has been a very important factor in my life. It has been a happy marriage. We had three children and we haven't had

The Sangers' wedding photograph, 1940 (courtesy of Frederick Sanger).

any crises and have had a quiet life together and have seen the world together too. She is a wonderful person. None of our children became a scientist. We have two grandchildren by the second boy. They're both interested in chemistry.

Of course, people can't just set out to win two Nobel Prizes. But they can set out to try to become a happy and satisfied scientist which you are too.

People who do set out to win Nobel Prizes never do very well. I think success in chemistry, and in science generally, depends on being interested in the work. Do what interests you. Most of the satisfaction is from the fun of exploring, doing things that nobody else has ever done before. That to me is much more exciting than winning the awards, though that is very nice too, and it helps one in one's career. I've certainly had a very good life.



François Jacob, 2000 (photograph by I. Hargittai).

6

François Jacob

François Jacob (b. 1920 in Nancy, France) is at the Pasteur Institute in Paris. He was awarded the Nobel Prize in Physiology or Medicine for 1965 jointly with André Lwoff (1902–1994) and Jacques Monod (1910–1976) "for their discoveries concerning genetic control of enzyme and virus synthesis."

After attending the Lycée Carnot in Paris, he studied medicine in Paris with the intention of becoming a surgeon. His studies were interrupted by World War II and Jacob joined the Free French Forces in London. He served as medical officer in Africa, participated in the Normandy invasion, and was severely wounded. He was awarded the Croix de la Libération, the highest French military decoration of the war. He is also Grand-Croix de la Légion d'Honneur. After the war, François Jacob completed his medical studies and submitted his doctoral thesis in Paris. He had to give up his intention of becoming a surgeon because of his injuries. In 1950, he joined the Pasteur Institute under André Lwoff and simultaneously obtained a science degree in 1951 and a doctorate in 1954 at the Sorbonne.

François Jacob worked mainly on the following subjects: genetic mechanism in bacteria and bacteriophages; analysis of bacterial conjugation; gene expression and its regulation; messenger RNA, repressor, operon, replicon, allostery, episome, and evolutionary tinkering. During the past decade or so, Jacob has studied the early development in the mouse embryo using mouse teratocarcinoma as a tool. His main goal is to analyze the regulatory circuits involved in the development and cellular differentiation of the early embryo.

He was appointed Laboratory Director in 1956 and Head of the Department of Cell Genetics in 1960. In 1964, he was also appointed Professor of Cell Genetics at the Collège de France. He served as Chairman of the Board of the Institut Pasteur between 1982 and 1988.

François Jacob is a Member of the Académie des Sciences, Paris (1977) and of the Académie Française, Paris (1996). His scientific awards include the Charles Léopold Mayer Prize of the Académie des Sciences (1962) and the Lewis Thomas Prize from Rockefeller University (1994). He is a Foreign Member of the Danish Royal Academy of Arts and Sciences, the American Academy of Arts and Sciences, the National Academy of Sciences of the United States, the American Philosophical Society, the Royal Society (London), the Académie Royale de Médecine de Belgique, the Hungarian Academy of Sciences, and the Royal Academy of Sciences (Madrid). He has received honorary degrees from several universities.

He has authored four books for a general readership. All of them have also appeared in English: *The Logic of Life: A History of Heredity* (1970), *The Possible and the Actual* (1981), *The Statue Within* (1987), and *Of Flies, Mice, and Men* (1997).

We recorded our conversation in Dr. Jacob's office at the Pasteur Institute on October 24, 2000.

You write in your book Of Flies, Mice, and Men *[p. 135] that scientific work is linked to the idea of progress.*

I'd rather say that progress is linked to scientific work.

What you meant in the book was that scientific work is eventually surpassed in time. In this sense I would like to ask you about the fate of your own scientific work.

That's a good question because I think it has remained valid although many people want it to disappear and have their own things instead. What we did here, in this group, was that we found the mechanism of gene expression. We proposed a model whose principle was that there is a regulatory gene, which makes protein, which acts on specific places of DNA, and it either activates or inhibits the expression of the neighboring genes. We worked on viruses and bacteria but hoped that the principle would be valid for higher organisms. It has been learned since that the principle is valid indeed with some complication as could be expected. The complication is that in higher organisms, instead of one single protein, there are many proteins, which interact and regulate the whole thing. The principle of the gene

making a protein, which act on a special DNA sequence and turns it on or off, depending on the systems of the addressee's sequences is valid throughout the living world. There are people, especially in the United States, that tend to forget these findings and advance their own work, replacing our words and expressions with their own to make it appear new.

You have been considered to be the theoretician of molecular biology. Is this a proper characterization?

I like theories and we theorized various things but I don't think of myself specifically as the theorist of molecular biology. Crick has at least as much theorized as I have.

You have also been compared to Linus Pauling and W. L. Bragg in that all three of you always "Wanted to have it all."

I can tell you what it meant. Pauling had made this important discovery on the structure of proteins and he wanted also the nucleic acids, but Francis [Crick] and Jim [Watson] got the double helix. In our work, we proposed a model in which the regulatory gene made a protein, which acts on other DNAs and we called it repressor. The next step in our work should have been to isolate this repressor. It was the work mainly of our chemists, but they failed, and I was not happy with that. We should've isolated the specific repressors that we were working with, and they were isolated by others, in Harvard, by Walter Gilbert and Benno Müller-Hill and by Mark Ptashne. So, we could not have it all.

Benno Müller-Hill had become interested in the problem when he had read your paper [F. Jacob et al. C. R. Acad. Sci. *1960, 249, 189–191] on the* lac *operon model. He wanted to work on this problem but was afraid to apply to your group; he rather opted for Bloomington, Indiana.*

He wasn't afraid of me; he was afraid of Monod.

Marshall Nirenberg, on the other hand, had applied to you but you did not accept him.

I remember it very well. I had very little room and could take very few people. Marshall wrote rather late and all my room was filled up and I didn't know him.

François Jacob in 1960 (courtesy of François Jacob).

Was there a French school of molecular biology, distinctly different from the others?

Yes, there was. We did mainly genetics here. I came here a few years after the war. I was heavily wounded in the war. Originally I had wanted to become a surgeon but because of my wounds in my right arm and leg it could not be. First I quickly finished my medical school training and tried various jobs in the movies, journalism, and ended up in research, and came to the Pasteur Institute. At that time Lwoff and Monod were working in the two opposite ends of the corridor. Lwoff was working in the physiology of bacteria and Monod was doing some mixture of physiology and biochemistry. We started doing molecular biology as a derivative of physiology, focusing on the properties of the bacterial cell. Lwoff was working on bacteriophage, Monod on the induction of enzyme synthesis, and with Wollman we started on the genetics of bacteria. We had a system in which we studied the movement of the chromosomes between what we could call male and female or donor and acceptor. The male chromosome is injected into the female and it moves at a constant speed and it is possible to map the movement of the chromosome by the time of its entry. It is the same when a train goes from Paris to Marseille at a constant speed; you can plot the position of the train at any given moment if you know the starting time and the speed. We had several different ways of looking at the introduction of

chromosome into bacteria, we could do genetic recombination or we could do mapping by time.

Ours was a fantastic system for playing with physiological genetics. Generally, when you do genetics, you have a male and female with markers, and you look at these markers after recombination, in the progeny. We had a new approach in that we could look at the gene expression before recombination. We could show, for example, that when we had what we called the prophage, a form of the bacteriophage genome in which the DNA of the phage is integrated into the chromosome of the bacterial host of the phage, as soon as it entered the cytoplasm of the recipient cell, it started multiplying. This multiplication started without genetic recombination. We could determine whether we had the gene controlling the synthesis of an enzyme, we could measure the time required to start the production of the enzyme once the gene was in the female. We could do rather precise kinetics on that and we could do the same thing with the regulatory gene. We had a system worked out by Monod: there was an enzyme, β-galactosidase, which was manufactured by the bacteria only in the presence of lactose of β-galactosides. Without it, the medium just did not synthesize the enzyme. We could combine a male, which had a gene, which managed to prevent the enzyme from being synthesized in the absence of lactose with a female, which did not have this gene, and see how it is expressed. In other words, we had a system, which allowed analysis of various bacterial functions. It was rather different from going straight to the gene-making sequences of DNA or the peptides.

You joined the Pasteur Institute in 1950, three years before the double helix. What was the atmosphere as regards the nature of genetic material at that point in time?

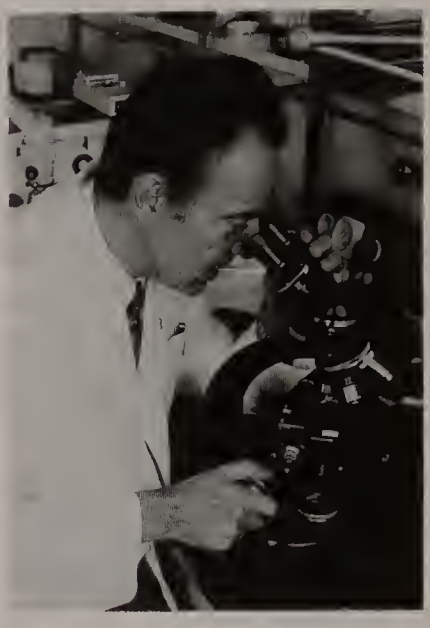
We were ready to accept that DNA was the substance of heredity.

Did it make a lot of difference when the double helix came about?

I was invited to attend the Cold Spring Harbor Symposium in May 1953. Jim Watson presented his model there and its importance was very clear.

It still took 9 years for the Nobel Prize.

The Nobel Committee never gave a prize to Oswald Avery. With the double helix, they probably didn't want to go too fast.



François Jacob at the time of the Nobel Prize, 1965 (courtesy of François Jacob).

In addition to Avery, has there been anyone else conspicuously omitted from the Nobel Prize?

It is difficult to say because the principle of the Nobel Prize is rather complicated. Every year there is more than one person or one group that deserve the prize. Avery's was an enormous discovery and I don't think there has been an omission comparable in magnitude ever since.

France has had relatively few Nobel laureates during the last decades.

Since the war, yes. There have been a few physicists and in physiology or medicine, there was only Jean Dausset in addition to us. Clearly, there have not been many important discoveries in France.

Any comment?

France is no longer such an important power in science as it used to be and there are several reasons for that. The structure of the French scientific system is not very favorable for scientific discovery. It is an old system, which has been progressively transformed after the war. We used to have the great professors to whom the students were afraid to talk. My first visit to the United States was in 1953 and I was extremely surprised by their relationship between professors and students. It was very

relaxed whereas it was very rigid in the European countries, perhaps less so in England.

Has it changed in France?

Slowly. It's still not what it should be.

Do you talk with young people here in the Pasteur Institute?

Yes, but the Pasteur Institute is much less formal and rigid than the universities. The records of the Pasteur Institute are also better for the Nobel Prizes than those of the universities. Molecular biology in France started here, the AIDS virus was isolated here, and it's much easier to start something new here than in a university.

I would like to ask you about your meetings with Leo Szilard.

I liked Leo Szilard very much. I probably met him for the first time in 1953 at this Cold Spring Harbor Symposium. He took me to a corner, took out a notebook, and began asking me questions. He forced me to answer him in his own wording. He had a special way of talking, which probably came from his physics. When we met a year or two later, he took out his notebook again and he checked my statements whether they were still valid. I was a very good friend with Aaron Novick and he was Szilard's student, so I saw Szilard a lot.

Recently, I asked Jim Watson, who appreciates Szilard a great deal, whether he would give a job to a Leo Szilard if he would show up at his doorstep? Would you?

Probably a special job of a bumblebee in a communication system whose task would be talking with people and getting and disseminating news.

Watson said that if another Leo Szilard showed up in his lab, he would probably not give him a job because Szilard was always two steps ahead of his colleagues and most people don't like that.

It would be interesting to have such a person around exactly because he was two steps ahead.

Your teacher was André Lwoff...

and he taught me that the art of research starts with finding a good boss.

How did you find him?

As I said, I had wanted to become a surgeon but I was wounded and spent a year in hospital because I had a hundred pieces of srapnel.

There are no visible scars.

I am covered with scars. I am also limited in motion of my right arm. It was impossible for me to become a surgeon. When I decided to go into biology, I tried to find a place to work. It took me a long time. I had good friends working in biology and I also read what I could. The only idea I gained from this was that something new was expected to happen in an area involving bacteria, biochemistry, and nucleic acids, genetics. This was the only thing I knew. My friends told me that there were two labs in Paris that were engaged in such research and that one was nicer and more pleasant than the other, and this was the Pasteur Institute. I came to Lwoff and told him that I would like to work with him. I also told him that I had an MD but knew nothing and I knew there was no particular reason why he should take me into his group. This was in September 1949, and he had no room for me. After that I came back every month to see Lwoff, and, finally, in June 1950, he told me that they found the induction of the prophage. I said it was fantastic, but I had no idea what it was. I looked it up and started to work here in September 1950.

What was your family background?

My ancestors came from Lorraine and Alsac, Jewish, and before that probably from Poland, Spain, Germany. In Lorraine our family records go back to the first quarter of the 18th century. My maternal grandfather was a student of L'Ecole Polytechnique and he became a four-star general, the highest rank reached by a Jew in the French Army.

Was it an assimilated family?

Very assimilated. My parents' families were very different in this respect. My father's family was quite active in going to the Synagogue while my mother's family had no such thing. My children have no interest in it as I did't have either, but, of course, they are aware of and identify with their Jewish origin. I described my difficulties in my autobiography

[*The Statue Within*, Unwin Hyman, London, 1988], the beatings and the fights in the school.

Did most of your fellow students participate in the war?

No, it was rather the exception. I left France in June 1940, joined de Gaulle in London, and became a member of his Free French movement.

I grew up learning that France was the symbol of resistance though lately I have understood that this was not quite so.

This was not quite so. For two years France was completely out. François Mitterand, for example, was a Petainist for a long time. When he was a young student he was a royalist. In the war he was taken prisoner but escaped and went to Vichy and became a functionair in Vichy. He joined the Resistance in the middle of 1943, which was rather late. The number of people who really started resistance early, either out of London or in France, was very small. De Gaulle distributed a decoration for people who were really active from the early days and there were about a thousand of which roughly half was posthumous. Today there are about 80 of us alive.

There were a few students of the first or second year of university studies, like me, who fought for five years, and when we came back, we did not want to go through the remaining years of our studies as if nothing had happened, we wanted to go directly to the examinations but they did not let me.

You have been interested in the artistic and esthetic aspects of science, but relatively few scientists of your standing have been.

I thought that many were. How about Josh Lederberg?

It was not my impression whereas he is clearly very interested in understanding his own career, in the way how he had become a great scientist. Of course, this is a legitimate question too.

It is.

There was one aspect of my conversation with him that made me feel let down. I asked him about his opinion of the Allies not bombing Auschwitz and the railway lines leading to it, and Lederberg explained

to me that bombing Auschwitz and the railway lines would not have been an efficient use of resources. I don't think so.

I don't think so either.

You were 24 in 1944. Did you know about the extermination camps?

I learned about them a little at the time of the landing in the summer of 1944. However, as early as in 1938 and 1939, I had already learned about terrible things going on in Germany from a German refugee who was giving me German lessons. He told me a lot about camps and the fate of Jews in Germany. It was not about the extermination camps but it was terrible too.

By 1944, the Auschwitz Report had reached the Western Powers and had become available for the Hungarian Jews also but by and large it was suppressed.

Do you think a genetic warfare is possible? Is it possible to develop biological weapons to kill a population selectively?

I don't know; for the present time I don't think so, but you have to wait to know more about the human genome. I expect surprises when the human genome becomes known completely. The notion of races may get a different interpretation, for example. We have to wait and see.

Cracking the genetic code was an important discovery. Were you anticipating it?

Here we started with the idea of the *messenger*, but we could not isolate it. Nirenberg was very lucky with his experiment. His boss at NIH was a very good friend of mine, Gordon Tomkins, a remarkable scientist and a remarkable musician.

Returning to your question about science and the arts, there is a lot in common between them at least in an initial stage. The role of imagination is similar in both science and art. At a later stage, however, they completely diverge. In art you don't have to confront what you imagine whereas in science you have to do an experiment.

If you don't make a particular discovery in science, someone else will make it, ...

That's right although it won't be exactly the same. There is style in science too. The style of Pasteur was something special. It was the style of the cavalry, concentrating all his forces at one place and trying to break through.

When you write about day science and night science, you mention the French garden in conjunction with day science but do not mention the English garden.

The French garden is always in comparison with the English garden.

Considering your books and your scientific discoveries, which will stay more influential, your books or discoveries?

I think the whole thing will be swept away by the general wave of life. Don't you think so? But there is also a difference between them. A scientific discovery is a stone in the wall whereas if you don't write the book, there is no book. As simple as that.

It's more difficult though for a good book to become obsolete.

It depends. I've written several books.

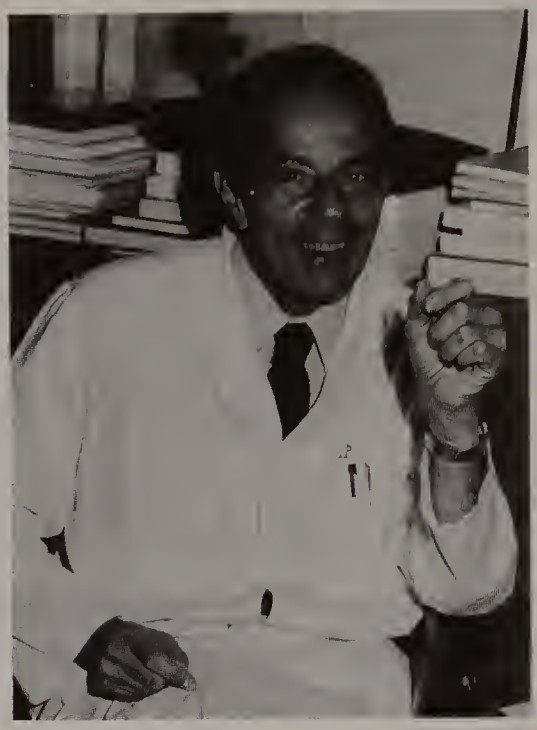
I'm familiar with The Logic of Life, The Statue Within, The Possible and the Actual, *and* Of Flies, Mice, and Men.

The Possible and the Actual is a small book but I like it. It's very difficult to assess the fate of books. In *The Logic of Life* I was seeking an answer to the question, "Why are we doing what we are, and not something else?" For this I had to look into history but I didn't read the historians of science, I looked to scientists and what they wrote. There are few people, except the historians of science, who look at the books by scientists of the 16th, 17th, 18th century.

Very few scientists wrote about the process of doing science. Kepler was one of the few.

But not many people read Kepler, except the historians of science.

Arthur Koestler's book about Kepler is accessible and has been quite popular.



François Jacob around 1985 (courtesy of François Jacob).

That's right, but it's 20th century. I met Koestler a couple of times. He was a strange fellow. He was talking all the time. The book he wrote about the Soviet system, *Darkness at Noon*, is a fantastic book.

May I ask you about your politics?

I don't do much politics. I try to follow what's going on but in France it's completely disparaging.

You never flirted with communism?

No. My family has been on the left, socialists. After the war, I was approached by several friends of mine who were members of the Communist Party and I went to a couple of sessions and was completely disgusted by how they decided for you what to think. Actually, that I went into genetics was in part because of Lysenko. Some prominent French communists, like the famous writer Louis Aragon, were for Lysenko, and so were several stupid professors of Sorbonne, without knowing a word of the problem of heredity.

You were elected to the French Academy of Sciences 12 years after your Nobel Prize.

We were rather hostile to the Academy, it was an old system, had too few members, they did not want to change their rules, so we were reluctant to announce our candidacy. Announcing your candidacy was a prerequisite of getting elected, which was quite different from other academies. Lwoff had been a candidate once but someone else got elected in his stead, which added to our ill feelings about the Academy. Lwoff and I were finally elected without our having announced our candidacy. By then Monod had died, so he was never an academician.

Now you are also a Member of the French Academy, which is quite exceptional for a scientist.

There I also refused to announce my candidacy but they elected me nonetheless, four years ago. It is too much selective, having a total of 40 members only with two or three scientists only. My function is to control the words used in biology and medicine.

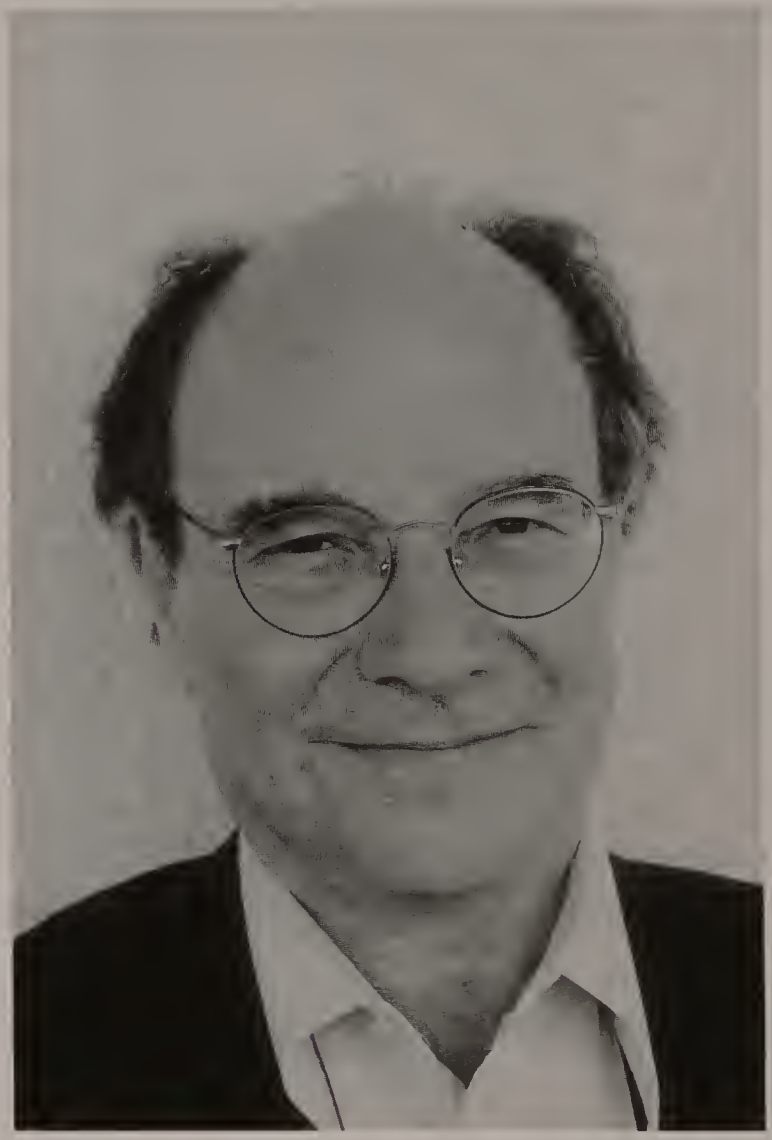
How much is the language a barrier today for French science in disseminating French results and in accessing foreign results?

There is a big fight about the English language, which is the common world language of science. The French don't like that and the Académie Française in particular doesn't like that. However, they have to cope with it.

What is your interest, what do you do nowadays? Please, describe a typical day of your present life.

I am more and more interested in biology. I am especially interested in the new developments of biology and its growing role in society. I am also interested in human rights of scientists. And also in literature and philosophy.

I go every morning to the Pasteur Institute where I have an office. There I read the scientific journals and discuss with colleagues and students. In the afternoon, I write at home.



Walter Gilbert, 1998 (photograph by I. Hargittai).

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Walter Gilbert

Walter Gilbert (b. 1932) is M. Loeb University Professor in the Department of Molecular and Cellular Biology of Harvard University. He shared half of the Nobel Prize in Chemistry for 1980 with Frederick Sanger of Cambridge University "for their contributions concerning the determination of base sequences in nucleic acids." (The other half was awarded to Paul Berg of Stanford University "for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA.")

Walter Gilbert got his B.A. degree in chemistry and physics from Harvard College in 1953, his M.A. in Physics from Harvard University in 1954, and his Ph.D. in Mathematics from Cambridge University (the subject of his dissertation was actually a theoretical physics project on "generalized dispersion relations for pion-nucleon scattering"). He has been at Harvard University since 1957 with a break for a few years when he was with Biogen, a biotechnology company. During his career at Harvard, Dr. Gilbert started out in physics, went on to biophysics and then biochemistry, and spent his longest period of time in biology. Since 1992 he has also been Vice Chair of Myriad Genetics, Inc.

Professor Gilbert is a Member of the National Academy of Sciences of the United States (1976), the American Academy of Arts and Sciences (1968), and Foreign Member of the Royal Society (London, 1987), among other memberships. He has received the Charles Léopold Mayer Prize of the French Academy of Sciences (1977), the Louisa Gross Horwitz Prize of Columbia University (with F. Sanger, 1979), the Albert

Lasker Basic Medical Research Award (with F. Sanger, 1979), and the Biochemical Analysis Prize of The German Society for Clinical Chemistry (with A. Maxam, F. Sanger, and A. Coulsen, 1980), and was New England Entrepreneur of the Year in 1991, among many other distinctions.

We met when we were both lecturers to the Frontiers in Biomedical Research meeting in Indian Wells, California, and recorded our conversation in Indian Wells on February 2, 1998.*

You have had a remarkable career, from theoretical physics to experimental biology, and winning a chemistry Nobel Prize. How did all this happen?

I became interested in science at a very early age. When I was 10 or 11, I was interested in chemistry. I collected minerals and was interested in amateur astronomy. My interest in science continued more passionately through my high school years. I spent a great deal of my high school experience playing hooky, going downtown and reading books on physics in the Library of Congress, in Washington, DC. I could get away with it because my grades were very good. I graduated in 1949 and was reading atomic physics. One of my high school projects was building a Van de Graaff generator. I was interested in inorganic chemistry at that time.

I went to Harvard thinking to become a chemist and became a chemistry and physics major, but my interest shifted during college toward physics.

When I went to graduate school, I studied theoretical physics. I studied at Harvard and then went to Cambridge for two years to study theoretical physics. My actual degree is in mathematics from the University of Cambridge, since theoretical physics is called mathematics there. My supervisor was Abdus Salam, who was a very good theoretical physicist and won the Nobel Prize in 1979. He died recently. But at that time he was just a young theoretical physicist. Then I came back to Harvard and continued in physics and took my degree by mail from Cambridge. At Harvard, I worked alone. Sheldon Glashow, who won a Nobel Prize in Physics in 1979, and I were roommates in the basement of the physics building at Harvard. After I got my degree, I became a postdoctoral fellow in physics for one year and then became Julian Schwinger's assistant for a year in

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an instructorship position at Harvard. Schwinger became a Nobel laureate in physics in 1965.

Then I went onto the Faculty in theoretical physics at Harvard and taught theoretical physics of all kinds for a number of years: quantum theory of fields, general relativity, electricity and magnetism, classical mechanics, in rotation, for about five or six years.

I got involved in biology because I'd met Jim Watson at a party in Cambridge in the fall of 1955. We became friends. This was two years after the DNA double helix discovery, and he had come back to Cambridge after having been away for a year. He came to Harvard as Assistant Professor in Biology, and I came back to Harvard, eventually as Assistant Professor in Physics. We remained friends and talked about what was going on in science. In the summer of 1960, the messenger RNA story began to emerge in his laboratory. I went to visit him in the laboratory, read a few papers, joined in, and worked with him on the experiments that, ultimately, led onto the discovery of messenger RNA. I continued working with him into the fall that year. The problem that we faced was to show that there was an unstable RNA intermediate that was copied from DNA and then used to make protein. The theories up until that time were that proteins might be made by an RNA but that the RNA code was stored somewhere inside the ribosomes. Then a line of experiments, first with T-even phage, began to suggest that there might be RNAs that were immediate copies of the DNA.

There was also a line of experiments from a French group, by Jacob and Monod, that suggested that there might be an intermediate and unstable RNA. We looked for that in our group and showed that there was an unstable form of RNA in bacteria that copied the DNA, went to the ribosomes, was used to make proteins, and then was destroyed. We did these experiments in the summer and fall of 1960 and published them in *Nature* in the beginning of 1961. This was my introduction to molecular biology.

Then I went back to physics for six months in the fall of 1961 and then returned to the biology laboratory and worked steadily in molecular biology. In the summer of 1961 we went to the biochemical congress in Moscow. That was the point where Nirenberg reported the "poly(U) makes polyphenylalanine" experiment. That was the first demonstration of a synthetic messenger RNA and the first break in deciphering the genetic

code. When I went back to Harvard, I started working on the mechanism of protein synthesis. I used synthetic messenger RNAs to work out more details of the way the messenger RNA went to the ribosomes and the ribosomes made proteins. Those experiments were successful. They showed that many ribosomes used a single messenger RNA and they also showed that the actual mechanism by which the protein chain grew was that the growing chain remained always attached to the last tRNA. The chain was end-activated. The activation energy stayed at the carboxy end of the peptide chain, joined to the tRNA, and the chain then could add a new amino acid brought up by a new tRNA. At that time, the fact that the chain grew from the amino end to the C-terminal end had just been shown by Howard Dintzis. How the chemistry was done, how the chain grew, how the pieces came together, was unknown until our experiments.

While I continued to work in biology, the Physics Department began to look very doubtfully at me. At that time, one had to be promoted to tenure within a five-year period. The assistant professorship was a five-year appointment, and in the fourth year you were either promoted or had to leave. When I came up for promotion, the Physics Department said that I was no longer working in physics so they wouldn't promote me. Luckily, Harvard found a way of creating an appointment, and I was promoted to tenure in biophysics. I then sat on the senior staff in both the Physics Department and the Biology Department. Those two departments functioned in an entirely different spirit.

The next thing I worked on in science was the genetic control mechanism. How does DNA function to make proteins? By the period I'm talking about now, the mid-1960s, the genetic code had been broken. I worked on issues like how accurately does the ribosome function? And how can one upset its accuracy? Then I became interested in trying to discover the nature of the control mechanism by which one gene controls another. The leading theory was the theory of Jacob and Monod that there were compounds, called repressors, which were the products of one gene that affected, controlled, the function of another gene. The mystery at that time was, what is the nature of these repressors? Are they protein? Or are they RNA? Or are they something else? That was a subject of considerable interest and considerable ambiguity, since there was no biochemical approach to these molecules. From about 1964 on, for several years, I was doing

experiments trying to identify the repressor. Most of these experiments failed, but then, with Benno Müller-Hill, we devised an experiment that finally succeeded.

Müller-Hill came to me as a postdoc, and we spent several years working together. We detected the *lac* repressor, which is made as only a few molecules in each bacterial cell, by detecting its binding to the inducer, a small molecule that, ultimately, deactivates the repressor. We did this by equilibrium dialysis. We made radioactive inducer and dialyzed it against extracts from the cells and detected an increase in concentration inside the dialysis sac. The end result of the experiments was that we could detect the product of a control gene, a protein made in very small amounts, about 10 molecules per cell. We purified that protein, characterized the molecule, and showed that it bound to DNA. When Benno went back to Germany, he got a faculty position and continued to work on the repressor, purified the protein in large amounts, worked out its amino acid sequence, and has continued to work on gene control to the present day.

Benno has written a number of books; he has a strong literary as well as a research interest. One of his books is about the behavior of scientists during the Nazi period. That book is called *Murderous Science*. He had a student who researched the archives of the Kaiser Wilhelm Institute. He had great problems getting that book published in Germany, because a lot of the collaborating scientists stayed in position after World War II and were very much involved in the German university system. Benno is very strong-minded, very outspoken.

How did you start your work on DNA sequencing?

We had a model of how the repressor worked by binding to DNA and blocking the RNA polymerase. I worked on the mechanism of DNA replication in the late 1960s. Then I went to Paris for a year, came back, and then, in 1969 and the beginning of the 1970s, we began to look at the issue of how did the *lac* repressor really interact with DNA. At that time the restriction enzymes had just been discovered, and we were busy in the laboratory purifying restriction enzymes and had begun to manipulate DNA by cutting it into pieces. I studied the DNA region that interacted with the *lac* repressor by putting *lac* repressor onto DNA and digesting the DNA with DNase. We observed that the protein protected a 20-base-long piece of DNA. We isolated that piece of DNA, copied the

fragment of DNA into RNA, worked out the RNA sequence, and deduced the DNA sequence.

It took us two years to deduce the sequence of the 20-base-long piece of DNA: the repressor binding target, called the *lac* operator. That was the first long DNA piece sequenced, and 20 bases is not very long. Then a student, Nancy Maizels, worked out 63 bases of the sequence of the beginning of the message made from the *lac* operon, and we found all the sequences of the mutations in the operator involved in the binding of protein.

At that point I was no longer working on the issue of "how do you sequence DNA." We had found all the sequences we wanted by copying DNA into RNA. Our actual sequencing method emerged as a result of an interaction with Andrei Mirzabekov, a Russian, who visited the United States two times in about 1974. He came to see me to talk about the problem of the interaction of proteins with DNA. He was using dimethyl sulfate as a reagent to distinguish between the major and minor grooves of DNA. Dimethyl sulfate is a methylating agent and methylates the adenines in the minor groove of DNA, but methylates the guanines at the N-7 position in the major groove of DNA. In principle, if one could detect where that agent methylated, one might be able to show whether the protein fitted in the major groove or the minor groove of DNA. Andrei had done such experiments with histones and tried to argue how they interacted with DNA. Andrei came to me and said, "You should do an experiment like this with the *lac* repressor." He came the second time and urged me again to do this experiment. I became enthused by that and visualized a way of doing the experiment. What I conceived was to realize that if one methylated the DNA that rendered the base unstable on the sugar. Then one could easily depurinate that methylated base by heating the DNA in a way that would not depurinate other sites of the DNA.

Once you depurinated DNA, you could break it at that point, because the sugar would be subject to β-elimination in alkali. Since we had fragments of DNA, cut out by restriction enzymes that covered the operator, we could design an experiment in which one could label the end of one fragment and break the fragment at the point at which the dimethyl sulfate attacked. Since we knew the sequence of the DNA, I put the repressor on the DNA, methylated the DNA, and recognized the site where the methylation occurred

by breaking the DNA there. If the repressor would block the methylation at a point, we expected to recognize that position, because methylation would not occur there, and in this way one should be able to see where the protein touched the DNA.

I tried this experiment. I decided to put a radioactive label at one end of the DNA fragment. I knew the sequence and could separate the broken fragments of DNA by size. I expected to be able to decipher where in the sequence the methylated base occurred. What I didn't realize was that the pattern was going to be so distinctive that when one looked at the pattern, one didn't have to know the sequence beforehand. The pattern was so distinctive that one could recognize the DNA sequence right on the gel and recognize where the adenines occurred and where the guanines occurred. That first experiment did two things: it showed in detail where the repressor actually touched in the minor groove and in the major groove, and it also suggested that one could get a sequencing method. In one single gel we could easily see the adenines at positions 31 and 32. Allen Maxam, who had been my technician for a long time, since we had done the first operon sequence at the beginning of 1970, and I then tried to round this out as a sequencing method. We had a way of detecting the two purines, and the first DNA sequence we did was by doing the purines on both strands and deciphering the sequence in that way. Then we looked for chemical methods that might damage the pyrimidines. In principle, hydrazine was such a reagent, and it could be used to damage the pyrimidines and thus lead to a break in the DNA at the pyrimidines. Then Allen found the salt effect, to distinguish between the thymines and cytosines. That was done by taking arbitrary things off the shelves and trying one after the other. All of these reactions were peculiar, because they were unpredictable in detail.

The logic behind the sequencing is interesting, especially for chemists. The sequencing that we devised is a completely chemical method. The non-DNA chemist's general view of DNA chemistry would be that the bases are very similar, "How could you construct reactions which would distinguish between them?" The trick is that, at the very beginning of the reaction, we react only a tenth of a percent of the bases with the reagent. That permits one to differentiate between reactivities by at least a factor of 10. The bases that have reacted are converted into entirely different chemical forms, which one can now attack with a harsh reagent. Thus, the harsh attack

on the DNA is done on a modified molecule. This breaks the problem into two, each of which is solvable. The behavior of the gels was also an important factor. This technology had emerged in our laboratory and other laboratories during the first part of the 1970s. In the background was the separation of DNA fragments by size, which was developed to analyze restriction-enzyme-cut DNA fragments. In Fred Sanger's case, he was pursuing biosynthetic methods, but, again, he ended up using the same gel resolution methods.

Was there any interaction between your groups?

We knew about the work of Sanger's group from their publications. We never tried Sanger's methods for DNA sequencing. We ended up with a chemical method which worked in a spectacular way; the gels worked beautifully. We could resolve 500 long DNAs on the gels. It was also an easier and cleaner pattern than one could get by the biosynthetic methods.

We distributed our method immediately. We talked about it at a Gordon Conference; we gave people handouts of how to do it. In those days no one thought of patenting. We published a paper describing the method, but by the time our paper appeared, probably more than 20,000 bases of DNA had been sequenced using our method.

A graduate student then sequenced the first complete protein gene, the *lac* repressor gene. Then we did the penicillinase gene by DNA methods. My students' theses went from 63 bases in DNA, done as RNA, to 1000 or so in gene sequencing, and then to 5000 for a plasmid, and that's when we gave up working on that problem.

Soon after that, I became interested in recombinant DNA techniques. This was in the mid-1970s, and I became wildly enthusiastic about the issue: "Can we make novel DNA structures?" I picked up, from the literature, a discovery from 1970 that one could use T4 DNA ligase to attach blunt ends of DNA together. That observation had been in the literature, but even people who had known about it thought it to be so inefficient that they didn't try it. The general thinking at the time was that one had to have overlapping ends in order to attach DNA molecules together. I showed that one can take a flat cut end of DNA and attach it to any other flat cut end of DNA very easily, and in very high yield, by just doing a reaction at room temperature. That technique opened up a whole new world of

tying DNA molecules together and making arbitrary new combinations. I got very interested in that process; I talked about it all over the country in seminars on DNA sequencing and about the possibilities of making new DNA molecules from DNA molecules of known sequences. We now had a simple way of tying arbitrary pieces of DNA together, to put start signals on human genes to make them function in bacteria. We developed "portable promoters." The DNA sequencing made it possible to know what we made when we constructed new genes in bacteria. I then had students try to make insulin in bacteria. Then my interest moved on from the original abstract question of "Can we make novel things?" to the biotechnology world of practical applications. Insulin from bacteria is an example of a useful, novel product.

This interest led me, and a number of other scientists, to set up one of the early biotechnology companies, Biogen. I got more and more interested in the practical applications of science in that period, from 1978, when the company was set up, to 1981 when I left Harvard University and started to run the company. Then in 1985, I left the company and went back to Harvard. In 1981, I had resigned from the university and in 1985, I was reappointed.

Since my return to Harvard, I've been involved in a number of small companies. I enjoy small companies. They are very exciting human structures as people come together to do something new. Small companies are really created by novel ideas. I have been involved in one company, Myriad Genetics, which looks for genes for common diseases. Myriad found the breast cancer genes two years ago by cloning two genes that predispose women to breast cancer. About 1 percent of women carry mutations in one or the other of these genes. The company is looking for other genes; genes that predispose people to heart disease, for example. When such genes are identified, they have two uses. One is that one can take that knowledge into diagnostics. The commercial structure of the company was built around the idea that such diagnoses will be very useful to the individual. For example, if you're a woman and you carry a breast-cancer-gene mutation, it's likely that you will have breast cancer before you have your first mammogram. One preventative thing you can do is to have early mammograms to detect the disease. Just that knowledge makes a major difference. If you knew that you had a gene for colon cancer (there are such genes, but they are not yet identified), then you would have a yearly colonoscopy. That

would be annoying, but it can detect the cancer early enough for effective treatment.

How does such a company get its returns?

By selling tests, to whoever wants to buy them. For breast cancer, a physician orders the test and an insurance company pays for it. The company has just introduced a test for high blood pressure. There is a specific mutation, and about 10 percent of the Caucasian population are people homozygous for that mutation, that will lead to a salt-dependent high blood pressure. If you have this mutation, and if you have high blood pressure, you have the salt-dependent kind. If you don't have this mutation and you have high blood pressure, it is not salt dependent. About two-thirds of the people that have high blood pressure are not salt dependent, but one third are salt dependent. Today if you have high blood pressure, you go to the doctor, and the doctor says, "Don't eat salt." You go on a salt-free diet and see whether it helps things. That's very annoying, and for two-thirds of the people, it doesn't do any good. For one-third of the people who have high blood pressure, it's going to do some good. The new test, CARDIARISK, tests your genes and you'll know at once. The test has other implications too, but this is the most obvious one. CARDIARISK started marketing just a few weeks ago.

This may sound naïve, but why wouldn't, say, the National Institutes of Health initiate and support such research and disseminate its results?

It's a reasonable question. However, my attitude is that research that has a clearly applied character might as well be subsidized by a company. The companies are structures, which can both subsidize research and capture the commercial value. A university department doesn't have the structure to capture the commercial value or even think about creating a commercial value. Furthermore, I don't want a university department doing research because it thinks it will have a commercial value, because that's a bad motivation for research. I really want the department to be doing research that it thinks has the greatest intellectual promise. That's a different notion from what makes a buck in the short term.

The research done in the genome project, sponsored by the government, is to identify genetic markers. The end result will be to find all the human genes, using a fine set of tools. The genome project will make those tools available. Such long-term, future-oriented research almost has to be done by the government. Once the tools become available, then it becomes possible in a commercial setting to say, "Maybe we should try to focus on the issue of finding the genes immediately associated with a disease." Seeing this structure being set up, the pharmaceutical companies come along and find it well worth putting 5 million dollars a year into looking for those genes, because once they are found, the company will soon be able to find a drug. The university doesn't do research at that level, because such work requires large numbers of people, technicians doing routine work, a factory, and so on. Research done for short-term goals is very often a brute-force mission-structured research that lends itself to a company structure. The research that we want in a university, we want to be intellectually challenging, done often by a single student, from which he or she can learn something and which has deep intellectual consequences.

This separation of basic, long-term efforts in the university and applied, short-term efforts in companies is not a hard-and-fast rule. The government sponsors lots of research in the medical schools that is very applied. All of the biotechnology industry evolved out of basic research. The DNA sequencing was done as basic research in a university; the first recombinant DNA work was done as basic research in the universities. However, the companies generally have short-term goals, and the long-range research in the universities creates new industries 20 years later.

Where do you place the discovery of the polymerase chain reaction (PCR) in this spectrum?

PCR is a technique. It could have been discovered anywhere. A lot of the development of it was done by laboratories all over the country as well as in the company in which the discovery was made. PCR turns out to have great commercial applications as well as great research implications. The original discovery, however, was not made because of its commercial use. It was an accident. Discoveries are made in companies, if they are open enough.

Between our work on DNA sequencing in the early 1970s and 1978 when we worked on insulin, the sociology of science changed. The attitude toward patenting had changed. In the early 1970s, one's view, as a scientist, was that it would be better for discoveries to be in the public domain. This turned out to be a bad idea because things in the public domain are not exploited. If you worked on a government grant, you couldn't patent a discovery even if you wanted to. By 1978, that all had changed; the government wanted the universities to have the discoveries patented, and Harvard wanted us to have our discoveries patented. Our insulin work was patented, and Harvard owned that patent. Then it was licensed to Biogen. In fact, that technology wasn't used very much until recently, and Biogen won a very large patent suit against another company and made a great deal of money and Harvard made money from that. However, it's not good for the universities to be caught up in commercialization fever, and it is a risky business anyway.

When you returned to Harvard, did you go back to your old department?

The Biology Department of Harvard had split into several groups. Originally, the molecular biologists and the biochemists had left, and I was in that group. In the mid-1970s, the people in cellular and developmental biology split off and created their own department, leaving behind the people who were mostly interested in evolution, ecology, and such topics. When I went back to Harvard, I'd left molecular biology and biochemistry, and I went back into cellular and developmental biology. When I left in 1978, the people in cellular and developmental biology thought that they had nothing to do with DNA; by the time I got back, in 1985, cellular and developmental biology thought that DNA was everything. Now we have a single molecular and cellular biology department, and, in about 10 years, all the departments of biology will fuse again. Two things happened. One was DNA sequencing, and the other was the recombinant DNA techniques to move DNA molecules around and to isolate genes. These techniques have dominated all of biology and are continuing to be more and more important. The techniques of molecular biology are being used everywhere, but nobody is doing molecular biology as a separate field.

How do you feel about cloning humans?

I'm skeptical that an adult animal has actually been cloned. There will be further technical difficulties in the cloning of a primate. On the other hand, I don't see the human cloning as very different from other methods now being used to permit childless couples to get children, like *in vitro* fertilization or donated eggs. If it does become possible to use a human nucleus to produce a genetic twin, I could see childless couples considering it. The "clone" is like a delayed twin, but has different mitochondria, a different womb, a different upbringing, and a different age. It would be one of those things that are done in certain cases.

Let's go back to the beginning. Was there any family influence in your becoming a scientist?

At the beginning I had a general interest in science. It was encouraged by my mother, who was a child psychologist who thought it wise to have her son interested in the sciences and her daughter interested in the arts. My sister, though, became a doctor. In any case, I came from an intellectual family. My grandparents came from Russia, the Ukraine, around the turn of the century, Jewish, their names got changed more than once, including on Ellis Island. Both of my parents were born in this country.

When I started as a freshman, I was most interested in chemistry, but I soon discovered that one could change fields in science. In college, I did physics and chemistry. In graduate school, I did theoretical physics. Then I was a physicist. When I changed from physics to biology that changed my view of functioning as a scientist. The whole view of the functioning of the world is different now from when I went to college. You didn't go into science because it was a well-paid profession. You went into science as a calling.

Did your parents witness your success?

Yes, they were still alive when I got the Nobel Prize, and I took them both to Stockholm.

Your present family?

My wife is a poet and an artist. She works in monotype, a printing process that creates dramatic, unique art. She just had a book of poetry appear, *An Ark of Sorts* by Alice James Press. We have two children.

You have made a remarkable tour in the sciences. It was not by design, I understand.

No, it wasn't. At the moment I'm an evolutionary biologist. I'm interested in what is called molecular evolution, using DNA sequencing. We now can trace the evolution of genes in detail, and I've set up models of how the first genes might have been put together in the first organisms. Molecular evolution traces connections between species around the world. This use of DNA has transformed all evolutionary systematics. This technique may be used to trace back the origin of humanity. That origin is now thought to be a small group, most likely in Africa, about 150,000 years ago. From there we then spread out all over the world. One can trace the patterns of human connections in greater and greater detail.

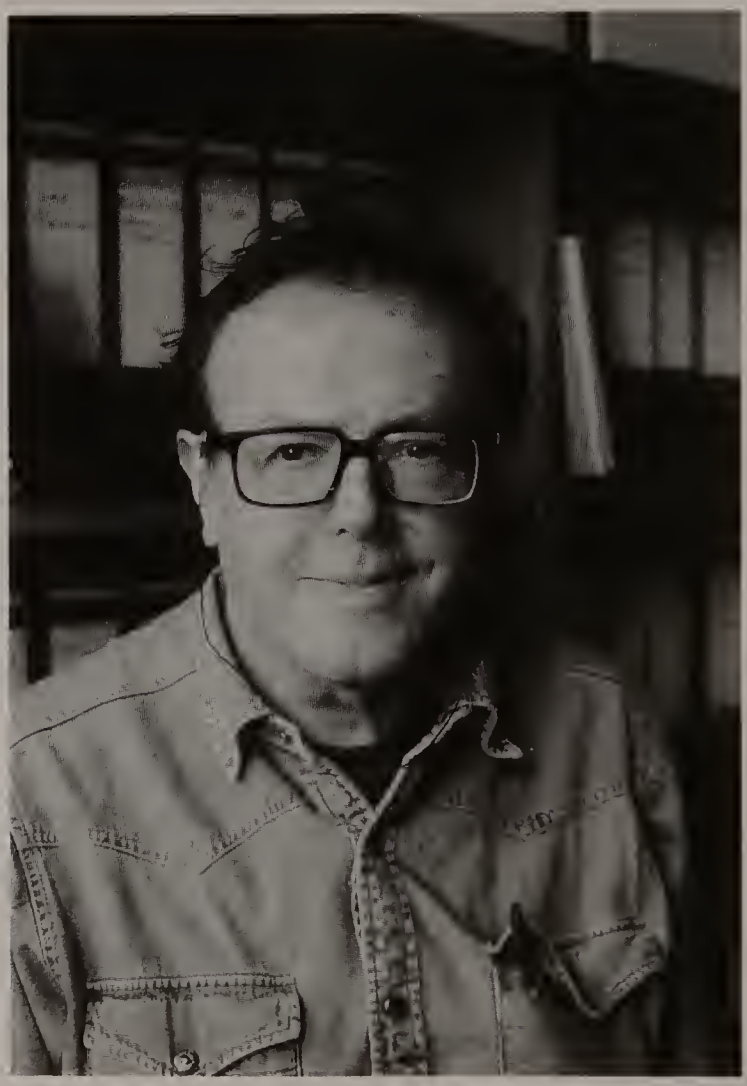
As a conclusion to this interview, any message?

My career may be a message about the usefulness of being educated broadly. The problem is knowing enough odd little things about the world. DNA sequencing depended on knowing, at a certain moment, a certain strange fact about the sugars in DNA. How did I happen to know that? It was probably some experiment I had been involved in, four or five years before. It would be very hard to follow the complete connection through. Edison used to say that being an inventor involves knowing all kinds of apparently irrelevant connections about the world.

The other message is that it's easier to change fields than one thinks. What handicaps people is that they've trained to do certain things, and they think they can only do what they've trained to do. This is basically untrue. The liberal education that the British used to use had the great advantage that by being trained for nothing, one felt free to do anything. If you read the classics, they obviously don't train you to do anything particular, but it is a training for the world in a fundamental way. One of the effects of the genome project on biology is that all the ways in which we used to do biology, the cloning and sequencing of genes, are going to disappear. Such things will no longer be research projects; they will just be something to look up. When I first did experiments with messenger RNA, we counted the radioactivity with a hand counter. Then the techniques got all automated, but now people are no longer using radioactivity at all.

There is constant change in the sciences, and if you don't realize this, you remain frozen behind. When I changed from a mathematical kind

of physics to experimental biology, I realized that in my work for my physics Ph.D., I learned an essential thing that was transferable. That particular ability was how to decide myself whether something was right or wrong. That was the crucial element, and that ability was transferable to another field. I had to learn the particular knowledge of my new field, but one can learn the particular knowledge of any field in a short time.



Benno Müller-Hill, 1999 (photograph by I. Hargittai).

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Benno Müller-Hill

Benno Müller-Hill (b. 1933, Freiburg, Germany) is Professor of Genetics, Emeritus, at the Institute of Genetics of the University of Cologne, Germany. He studied chemistry at the University of Freiburg and at the University of Munich and got his Ph.D. in 1962 in the chemical laboratory of the University of Freiburg. He did postdoctoral work in Howard Rickenberg's laboratory at Indiana University in Bloomington and in the laboratory of James Watson and Walter Gilbert at Harvard University. In 1968, he returned to Germany and joined the Institute of Genetics of the University of Cologne as full professor. At Harvard University, Dr. Müller-Hill isolated the first transcription factor, the *lac* repressor and he has worked on it ever since. He wrote a book on it: *The* lac *Operon: A Short History of a Genetic Paradigm* [Walter de Gruyter, Berlin and New York, 1996]. This book is a unique combination of modern science, science history, and personal anecdotes.

Dr. Müller-Hill is also well known for his research into the history of genetics in Nazi Germany, which is infamous for heinous crimes against humanity, and the silence surrounding this history in post-war Germany as well as in today's Germany.

Our conversation took place in Professor Müller-Hill's office in the Institute of Genetics on June 18, 1999. There are some names of German organizations in the text for which explanatory notes follow the interview text.*

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In my interview with Walter Gilbert, he mentioned your work on isolating the lac *repressor, which is so important in the genetic control mechanism [see, preceding interview in this volume]. How did you get interested in this problem?*

I got interested in the problem in 1960. I was a graduate student at the University of Freiburg in the laboratory of Kurt Wallenfels. We used to have a seminar on the literature and we read a short paper by Jacob and Monod [Jacob, F.; Perrin, D.; Sanchez, C.; Monod, J. "L'opéron: groupe de gènes à expression coordinée par opérateur." *C. R. Acad. Sci.* **1960**, *249*, 189–191], in which they proposed the *lac* operon model. The paper was in French but most of us could read French since Freiburg was in the French occupation zone. I was absolutely fascinated by this paper. At the seminar a microbiologist postdoc called the paper typical French hair-splitting nonsense. He was ignorant of the genetic findings on bacteria and his ignorance was typical of many in his field at that time in Germany. Professor Wallenfels did not want to commit himself in the discussion. All this prompted me to go for a postdoc, in 1963, with Howard Rickenberg in Bloomington, Indiana. Rickenberg had isolated the first permease in Monod's lab in Paris.

Why didn't you go to Paris?

I had attended a lecture by Monod some time before. I was shy and he seemed very arrogant intellectually. I did not dare to ask him. Also, Bloomington had great traditions, there was Luria before, and the most famous of all was H. J. Muller, who impressed me very much. He was just about to retire but he was still in the lab and came to the seminars. Haurowitz was also there, in biochemistry.

It so happened that Wallenfels had a NATO grant for a joint project with Rickenberg. It was for a totally absurd project but nobody minded that I used it for doing something else. I wanted to work on the specificity of the *lac* operator system.

Wallenfels was a sugar chemist and he had a lot of sugars that were not available commercially. They had been synthesized by his students. Before I went to Bloomington, I'd collected a small amount of every sugar there was in the lab, and then I tested these sugars with the *in vivo* system in Rickenberg's lab. It was a nice piece of work and it also led to some new techniques involving sugars that could be used for selecting mutants. I spent two years in Rickenberg's lab and tried to isolate the *lac* repressor. I spent about half a year on this and failed.

I wanted to continue these efforts and was looking for a job. I went to the International Congress of Biochemistry in 1964 in New York, thinking of getting into Jim Watson' group at Harvard. When I went to his lecture, it was impossible to get into the lecture hall, it was overflowing. I thought I'd just give up. Somewhat later that day, and quite depressed, I was wandering in the building where the meeting was being held and, suddenly, I noticed Jim Watson standing alone, lonely. I asked him whether he could take me on as a postdoc. I told him about my interest in the *lac* repressor. He directed me to Walter Gilbert, whom I'd never heard of. Gilbert had me come for an interview at Harvard, and I told him that I had tried, in vain, to isolate the *lac* repressor, and he told me that he had tried too, and he offered me a job. I was extremely lucky and I may have been the only postdoc, in this decade ever, paid by him.

What was your background?

I had studied chemistry in Freiburg and Munich, and had done my Ph.D. in chemistry in Freiburg. However, I'd deserted organic chemistry and was, *de facto*, doing enzymology at the Department of Chemistry in Freiburg.

After Harvard, I came back to Germany, accepting an offer for a full professorship at this Institute in 1968. This institute was opened in 1962

Benno Müller-Hill in the Bio Labs at Harvard in 1966 (courtesy of Benno Müller-Hill).

by Max Delbrück. Niels Bohr was the main speaker at the inauguration. Delbrück came back from America for two years and had a whole group of young people with him. When he left, almost everybody left too, and I was one of the first people among the new group that was hired.

In the 31 years that you have been here, have you done anything as important as your work in Gilbert's lab?

Yes, if we count my students' work too. The distinction is important. In Watson's lab at Harvard, of which Gilbert's lab was a part, they had a policy that they weren't coauthors if they did not actually participate in the work, in the experiments. I followed the same policy for 10 years before I gave it up.

The most important work was probably that done by my student Jie Kang. He isolated a cDNA clone coding for the precursor of the Alzheimer amyloid, a protein of about 700 residues. It opened up a new era of Alzheimer research. Typically, we did this and then left the field. The next step would have involved a large group and joint work with clinicians. For this work I was on the paper because by then I'd abandoned my original policy.

Another publication from my group, and one that did not carry my name, reported the first protein sequence of a repressor. For more than five years, it was the only *lac* repressor whose sequence had been determined. I had developed a technique for getting large quantities of the material, we made 11 grams of it. At that time you needed a lot of substance to do sequencing. It sounds insane today.

Then, on a totally different level, I found the records of the Deutsche Forschungsgemeinschaft during the Nazi time. These records had supposedly been lost but I found them.

How did you find them?

As usual, by accident. About 1981, I discovered that there was an incredible history of German human genetics during the Third Reich, which was completely pushed under the rug, and was not touched by anybody. If you take any book on the history of genetics written before 1984, you find no trace of it. Some "unheard of experiments" may have been mentioned but never a name, never any detail, never anything. There was only total silence, and not only German silence but total international silence as well.

I found the records where they should be, in the Bundesarchiv in Koblenz. This is for the period of 1933–1945. Although I had been thrown into

this by accident, I decided to investigate these records and write a history of German human genetics for this period.

What does "the records" mean in this case?

The grant applications, the evaluations, the responses to the applications, and the reports from the grantees. Some of the papers were indeed lost but a large number of them are still in the Bundesarchiv.

One of the most damaging things I found was the evidence documenting the collaboration between von Verschuer, a famous professor, and his postdoc, Josef Mengele. Von Verschuer was dead by then and the general claim was that he had had a vague relationship with Mengele but nothing real close. I found the documentation of von Verschuer's grant application to the Deutsche Forschungsgemeinschaft, asking for money to pay for the research his postdoc Mengele carried out in Auschwitz.

Are you saying that the experiments Josef Mengele did in Auschwitz were considered as his research by the Deutsche Forschungsgemeinschaft?

This is exactly what I am saying. It was a project for which an application had been made to the Deutsche Forschungsgemeinschaft and to which the Deutsche Forschungsgemeinschaft had agreed, and the Deutsche Forschungsgemeinschaft received one page biannual progress reports on Mengele's work.

Are you saying that Mengele was performing his crimes in Auschwitz under the auspices of the Deutsche Forschungsgemeinschaft?

Certainly. He was also counted as a guest and collaborator of the Kaiser Wilhelm Institute for Anthropology in Berlin-Dahlem during his entire tenure in Auschwitz. There was a tight connection between von Verschuer's Dahlem Institute and Auschwitz, and Mengele made several visits to the Dahlem Institute from Auschwitz.

You must have written about this.

I have. Here is the latest edition of my book, which appeared originally as *Tödliche Wissenschaft*, in German, in 1984 [Rowohlt Taschenbuch Verlag: Reinbek]. The latest English Edition of this book is *Murderous Science: Elimination by Scientific Selection of Jews, Gypsies, and Others in Germany, 1933–1945*, by Benno Müller-Hill [Translated by George R. Fraser, Afterword

by James D. Watson. Cold Spring Harbor Laboratory Press, New York, 1998].

What was the reaction to your book?

In Germany, silence.

No protest?

Silence. Here is then a new manuscript of a paper, "The Blood from Auschwitz and the Silence of the Scholars." The Max Planck Gesellschaft had recently had a conference on its own past, I was also invited, and I compiled this manuscript for the volume they are planning to publish. However, they informed me that they cannot accept my manuscript because they found it too long.

I've read that various organs, including brains, of people killed in concentration camps were sent back to Germany and those brains are still in Germany.

About 70,000 mental patients were murdered and their brains were sent to various institutions. Brains were sent back from concentration camps too, but this is not well documented. This problem has been investigated in Vienna. There was an anatomsist who had a close relationship with the Nazis and he must have received corpses and brains also from concentration camps, not only from insane asylums. This investigation was pushed by William Seidelman, a dedicated MD, working in Toronto.

In Germany there has been a massive use of the brains from insane asylums. The most outrageous thing was — and you can read about it in my book — that a Professor Hallervorden, who was very highly respected and who died as a member of the Max Planck Gesellschaft, received 700 brains until the end of 1944. It is documented that he went, at least once, to one of the extermination centers and was present when the children whose brains he wanted to analyze were being killed by gas. He showed how to take out the victims' brains fast, after the killing. Nothing ever happened to him. He was highly regarded and highly respected internationally.

Did the findings of these people get into the scientific literature?

Take, for example, Hallervorden, who was a brain specialist. He published about 20 papers based on such material, and these papers are sound, whatever

meaning the word "sound" may have in this case. So his findings went into the scientific literature.

There is a supposition that if you lose all sense of what's right or wrong, you may then also be completely deluded in science. I don't know how valid this is, but the case of Mengele and von Verschuer is a real case. It was known by then and it is known now that people of different races have different susceptibilities to various infectious diseases. For example, Ashkenazi Jews are less susceptible to tuberculosis than ordinary Poles. What Mengele and von Verschuer wanted to do was to find the molecular reason for this. They got very excited when they heard about a biochemist by the name of Alderhalden who had, in 1908, begun claiming that humans and animals make specific proteolytic enzymes when you inject them with certain bacteria and viruses. These would be a kind of antibody with proteolytic activity capable of cutting the other protein at specific places. This was the claim. Abderhalden called these proteins defense enzymes. The whole story about the defense enzymes was a delusion. They do not exist.

The man who claimed the existence of defense enzymes became a professor in Halle in 1911. He was highly respected in Germany and in Europe. Although some people doubted the validity of his discovery, nobody dared to say that this was an illusion or fraud. He told many people about his experiments that, in reality, did not work. There's a story about him and one of his postdocs. This postdoc couldn't repeat a certain experiment and told Alderhalden, but Alderhalden said that if it had worked once, that should suffice.

Alderhalden bewitched the scientific community into believing that these defense enzymes existed. Von Verschuer believed that the difference in the Ashkenazi Jews' resistance against tuberculosis could be found in these defense enzymes. The test was to take sera from Ashkenazi Jews and other people, infected and non-infected, and compare the amounts of defense enzymes. He went so far as to believe that these defense enzymes could then be used for therapy. Mengele collected the sera and sent them to Berlin to von Verschuer's institute. Von Verschuer himself was not a good biochemist but there was an expert of defense enzymes in the institute of the Nobel laureate A. Butenandt, and this expert did the tests. Butenandt later became the President of the Max Planck Gesellschaft, after the war.

Did you ever talk with him?

I did. He told me that he heard about it for the first time from me. To me the lesson of this particular case is that once you lose all morals,

you lose all intelligence, you lose your ability to critique, you don't check things any more. This is the best example where total ruthlessness goes together with the lack of scientific intelligence.

Were there other studies of similar origin, that is, crimes against humanity, whose conclusions were not a delusion and that survived?

What has survived, in a different manner, and to which we don't have access, is a Japanese project on biological warfare. It began in 1932 and ended in 1945. The Japanese murdered more than 10,000 people for this project in China. After the war, the Americans bought the data and the lab journals and promised not to prosecute the authors. If the Americans were willing to pay such a price for the information, you just have to suppose that the information was of value to them.

The silence after the war is especially frightening.

Many people knew about the connection between Mengele and von Verschuer but it was never investigated and von Verschuer went on to become a most respected professor in Münster and honorary member of various scientific societies.

Has he lost this respect after your revelations?

I doubt it.

Have you experienced any difficulties?

No real ones. Butenandt wanted to sue me but, alas, he did not. My book, *Murderous Science* was reviewed only once in Germany, by the *Frankfurter Allgemeine.* Of course, my book dealt with human genetics only but it had real names. It did not deal with medicine and it did not deal with psychiatry in depth. My book was the first, in 1984, but it was followed by many other books in Germany. The authors were not historians of science or medicine. Today there are still difficulties in carrying out this kind of research. For example, the Butenandt letters in the Max Planck Archive will not be available for investigation until the year 2025. Skillful and absolutely misleading usage of language also hinders uncovering the truth. The infamous human experiments in Auschwitz can be referred to as "medical tests." The blood samples were sent back to Germany from "the hospital" of Auschwitz. Perhaps the most upsetting is the usage of "patients," referring

to Jewish and other victims of Auschwitz. In the fall of 1998, I wanted to examine some documents in the Institute of Human Genetics in Münster. This is where von Verschuer became professor and director after a few years' break in post-war Germany. The present director of the Institute, Jürgen Horst, informed me that I could not do this examination of the papers because my getting access to these documents would jeopardize the rights of von Verschuer's former patients.

What has been the most important impact of your book?

It's no longer possible to pretend that it did not exist.

Was there anything in your background that pointed you in the direction of doing this research?

My father was a lawyer in Freiburg. My mother was Swedish. The Hill part of my name comes from her. My maternal grandfather was an Englishman who lived in Sweden. My mother was one of three daughters and when my grandfather died, my grandmother traveled through Europe, after World War I, in order to find husbands for her daughters. She found one for my mother in Freiburg. I was born in 1933. I was a child in the Nazi period.

Benno Müller-Hill with his father, W. O. Müller-Hill (courtesy of Benno Müller-Hill).

In 1943, I entered Jungvolk, which was obligatory until you were 14. From 14, there was the Hitlerjugend.

Did you talk about these things at home?

It was so awful that we preferred not to. But I was aware of the fact that my father was not a member of the Nazi party and that he listened to foreign radio. He was a sportsman, a mountain climber. During the war, he was an army judge in the Wehrmacht. He kept a diary, which I saw much later. His diary is a devastating account of what he saw and experienced. At the beginning he was in France, then in Russia. Then he became sick and was returned to Germany and spent the last part of the war in Strasbourg. According to his diary, he tried to give very lenient sentences, especially avoiding the death penalty that his colleagues favored a great deal; and some of them sentenced German soldiers to death for almost anything. After the war, my father became a public prosecutor in Freiburg. My parents were atypical and they had atypical friends.

Did this cause any problems for you? Children don't like to be different.

It was complex. For example, my mother insisted on our speaking High German at home and on not using bad words. Most of my friends were lower-class people who spoke dialect and used bad words. I had to live between two worlds.

In the Jungvolk I was in a special unit supervised by an SS man. Our subunit consisted of 10 children. We were being prepared for war and it was awful and at one point our subunit had a mutiny. The leader of our subunit, a boy somewhat older than us, came to our homes to pick us up and return us to the training. We beat him up. We were expecting the worst but the Allies bombed Freiburg and nothing happened to us.

What turned you to science?

I wanted to study law but my father would not support me in doing so. He thought I would make a too strict judge. He had a physical chemist brother so if I could not follow my father, I thought I would follow my uncle and decided to study chemistry. I stayed in my parents' home and became a student of the University of Freiburg.

Did you have any remarkable professor there? Was there anything that shaped your interests?

The philosopher Heidegger was still around. Although I despised him, I could go to his lectures.

I was a member of what was called SDS, the Sozialistische Deutsche Studentbund, a small group of students, half social democrat, half communist. The focus of our discussions was the Nazi past and the involvement of the university in it. There were about 10 of us, a totally atypical group. One of us was a Jewish student who survived. Another is the present mayor of Freiburg. His uncle had been in Dachau. At that time it was considered outrageous to look at the past of the university. You weren't supposed to touch it. Thus, in a sense, I was predisposed, when the opportunity came later, to look into the Nazi past of my science.

Are you a lonely person?

Not really. I had my friends in the SDS circle. Then, when I went to America, there was the Vietnam War and my friends there were involved in the protests. We went to demonstrations. It was also a very productive activity for my science because we were talking about science all the time during these activities.

What was the environment like here at the Institute of Genetics of Cologne University?

This institute differed from the rest of Germany, it was atypical, and I felt comfortable in it, and I didn't care about the rest of the university.

What is the highest recognition you have ever received?

I have never received recognition in the form of prizes. I am Honorary Fellow of the Hebrew University. I am a member of EMBO, HUGO, and the Academia Europaea, and I have also received some awards from France.

Anything in Germany?

No, never.

Would you care to tell us about your present family?

My wife teaches French and history. We have two children. Our son we named Jakob, from the Bible, after the first geneticist. I consider Jacob the first geneticist because of a story in the Bible. When Jacob wanted to leave,

Benno Müller-Hill, his wife, Rita, and their children, Sarah and Jakob (courtesy of Benno Müller-Hill).

his father-in-law told him that he could take with him the sheep that have dark spots. Jacob saw in his dream a dark male animal mounting a white female animal. Then, in my interpretation, he started crossing extensively, the whole herd, which after a while became all dark.

Our daughter we named Sarah, which is a beautiful name. It's also the name every Jewish woman had to have in Nazi Germany. I thought it was the time that people should be able to use this name freely. Incidentally, Sarah has become a popular name in Germany, without most people knowing about its origin.

Our son is 18. He just graduated from the gymnasium and is going to be in the army for nine months before going to university. He is planning to study physics. Our daughter is 22 and just finishing a three-year training as a nurse. She plans to study medicine. Our children were not baptized and this made it almost impossible for our daughter to have a career in the medical profession. Most hospitals are run either by the Protestant Church or by the Catholic Church. They hire you only if you are baptized. If you are not baptized, that may even be worse than being Jewish, that's the absolute bottom. So it was extremely difficult for her to find a place to get her training. She was the first person that the hospital where she

is working now took who was not baptized. Of course, they are not interested in her beliefs and she had been advised to go to an understanding priest who would baptize her quickly. But she refused that. There are state hospitals but much fewer and none in small towns.

I would like to ask you, as a geneticist, about the relationship between genetics and intelligence. It seems to be a taboo topic.

You're not supposed to talk about it. There's a total misunderstanding about it even among scientists, which is the following. If you could show that there are genetic differences related to intelligence, that some ethnic groups have more favorable genetics for intelligence than other groups, or the other way around, this would, *per se*, invite the accusation that you are attacking the losers. This is a total mistake. We have to face reality that such differences may exist but you should never use the information about such differences for the purpose of attacking people. We should distinguish between knowledge and what you do with this knowledge.

The main problem is that you have to have a hard definition of what is called intelligence. Great difficulties begin here. The psychologists and the psychiatrists are simply unable to deliver really hard definitions. Since there is no such definition, you cannot do genetics.

According to some, despite your diverse contributions to science, it's likely that you will be remembered for one thing only. Would you mind being remembered more for your anti-Nazi studies than for your genetics?

I would hope that the isolation of the *lac* repressor will also count. When I came to Wally Gilbert's lab, it seemed to be a solvable problem, and I wanted to solve it very much. It also seemed to be a problem where you could put in all your efforts with a fair probability of failure. Normally, when you do science, even if you don't achieve your original goal, something else may come out of your efforts, which you can publish. In this case, however, it seemed to be all or nothing. This was so not only for me but for Wally as well. At the time, he was teaching theoretical physics and he didn't have tenure at Harvard. So we were both having high stakes in this project. He didn't have many publications because he followed Jim Watson's policy of not putting his name on a paper unless he was involved in the experimental work. He had about eight graduate students and he

was showing them how to do the experiments but he was never a coauthor. This is very good for the graduate student, for developing independence and responsibility, but may not be very good for the professor's formal productivity.

Doesn't this approach downplay the intellectual contribution?

It does, the intellectual contribution disappears, and what counts is only what you do. On the other hand, this approach also implies that if you have a really good idea, you should also do it.

Wally and I talked a lot but didn't really know how to attack the problem. Then one day somebody came from Paris and told us that he'd solved the problem. Actually, he did not but for us it had a shocking effect.

The *lac* repressor was a notion and we wanted to isolate it and have the actual molecule in our hands. Supposedly, it was a protein in extremely low concentrations. My idea was that we could use a particular mutant of the gene, which produces this repressor. Finally, I produced this mutant, Wally tested it, and it worked but it was like walking on thin ice. Other people tried to get it too but, fortunately, they did not succeed before we did. Our first publication appeared in December 1966 in the *Proceedings of the National Academy of Sciences*. I've never lived in such an atmosphere of excitement and hard work ever since. We gave our utmost to the project.

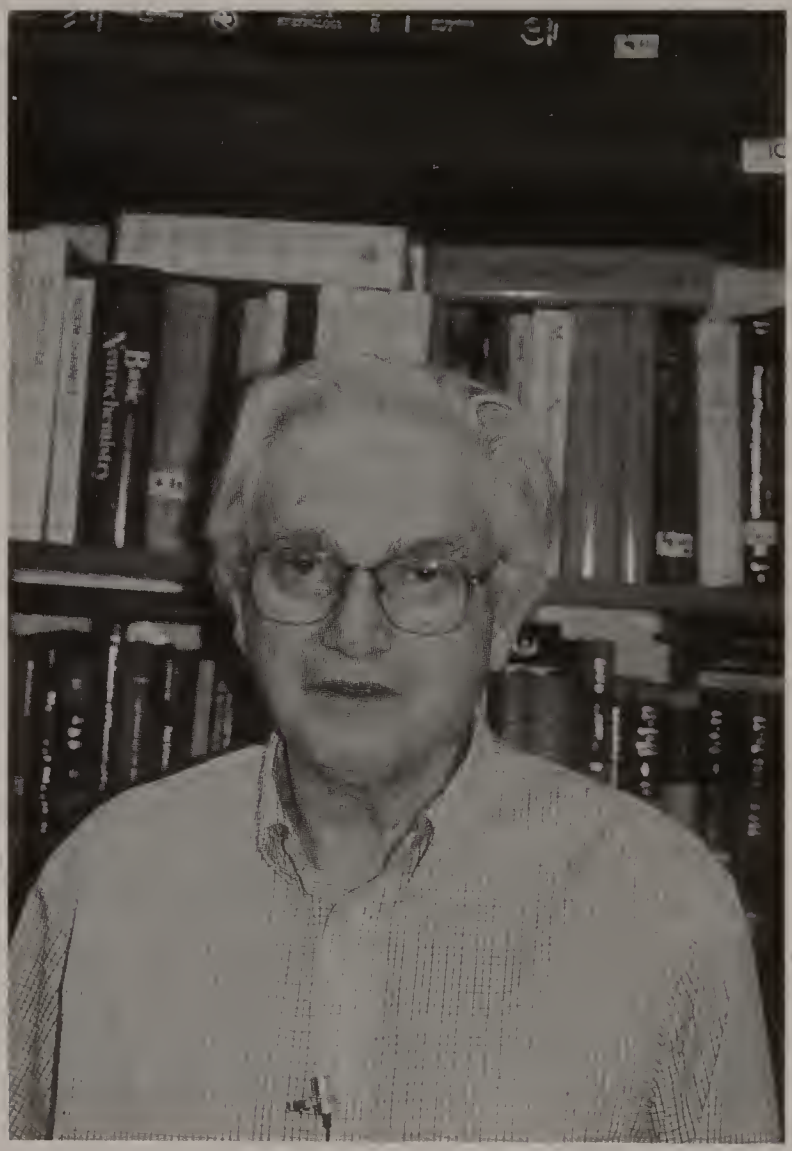
On the one hand, there was Wally with whom I could discuss the experimental details, and he loved to talk things over. On the other hand, there was Jim Watson, who did not talk at all. When he came into the lab, you would say one or two sentences, and that was it. You just realized that there was nothing more to say. For example, once I got a particular mutant and I was very proud of that but you can explain such an experiment in two minutes. There was another German postdoc there whom I knew from Freiburg, Klaus Weber. We had a bet about who spoke how much with Jim. After half a year, he was at 22 minutes and I was at 17 minutes, total. Jim Watson's non-speaking was even more driving. It had the effect that there was someone with whom you could speak only if you had something to say. If you had no result, there was nothing to speak about.

Listening to your description of your work on identifying the lac *repressor at Harvard, I feel an even greater appreciation for your tremendous work and self-sacrifice in uncovering the history of Nazi science.*

I would like to simply say that finding these records and writing on them was equivalent to what I did with Wally Gilbert. I found something unique and I had to do it.

Notes

Bundesarchiv, the Federal Archives of Germany, then in Koblenz, Germany.
Deutsche Forschungsgemeinschaft, German Association for Scientific Research; it is the counterpart of the National Science Foundation in the United States.
Max-Planck-Gesellschaft, The Max Planck Society, the postwar name for what was formerly the *Kaiser-Wilhelm-Gesellschaft zur Förderung der Wissenschaften* (The Kaiser Wilhelm Society for the Advancement of Science).
Reich, Empire; the Nazi state was known as the Third Reich.
Wehrmacht, The Armed Forces of Germany (today, *Bundeswehr*).



Marshall W. Nirenberg, 1999 (photograph by I. Hargittai).

9

Marshall W. Nirenberg

Marshall Warren Nirenberg (b. 1927) is Chief of the Laboratory of Biochemical Genetics, National Heart, Lung and Blood Institute, National Institutes of Health (NIH) in Bethesda, Maryland. He received his B.S. degree in zoology and chemistry in 1948 and his M.S. degree in zoology in 1952, both from the University of Florida, and his Ph.D. degree from the University of Michigan in 1957. He has been at NIH since 1957 and has held his present position since 1966.

Dr. Nirenberg received the Nobel Prize in Physiology or Medicine in 1968, sharing it with Robert W. Holley (1922–1993) of Cornell University and Har Gobind Khorana (b. 1922), then of the University of Wisconsin, "for their interpretation of the genetic code and its function in protein synthesis." He has been a Member of the National Academy of Sciences of the United States, the National Academy of Medicine, the Pontifical Academy of Sciences, and others. He has received the Molecular Biology Award of the National Academy of Sciences (1962), the National Medal of Science (1965), the Prix Charles Léopold Meyer (French Academy of Sciences; 1967), the Lasker Award (1968), and many other distinctions.*

Dr. Nirenberg first made the announcement of the "first word to be identified in the genetic code: 'One or more uridylic acid residues [poly(U)] appear to be the code for phenylalanine' " to the Fifth International Congress

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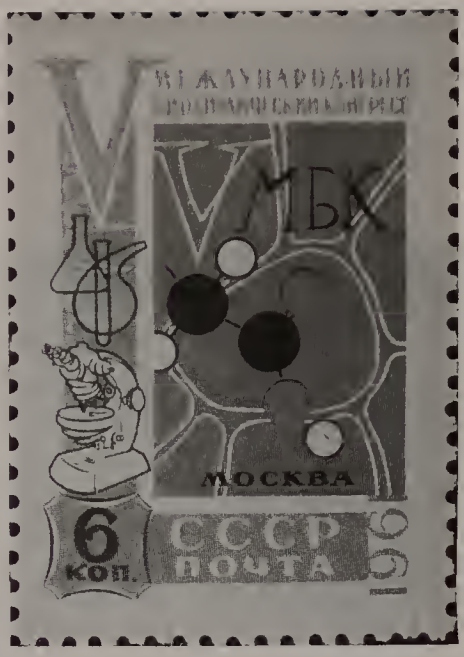


Soviet stamp commemorating the International Biochemistry Congress, Moscow, 1961.

of Biochemistry in Moscow in 1961. That announcement catapulted him to fame and recognition.

Marshall Nirenberg's autobiography is one of the shortest on the Nobel web site. I wonder if Marshall Nirenberg opens up often. I think not. So I felt privileged to be able to spend the afternoon with him on April 1, 1999. As we met in the hall outside his laboratory, I recognized him at once from a 35-year-old photograph. He had not changed much, except that his dark hair had turned white. As we started talking in his cluttered and windowless office, he made me feel comfortable, as if I had known him for a long time.

Nirenberg puts down his ideas every night in his notebooks. So far he has collected thousands of ideas in 40 volumes, which he is going to donate to the National Library of Medicine. Nirenberg compares his ideas to darts thrown at a target on the wall. You not only cover the target but you cover the entire wall with darts. A few of them, though, will hit the bull's-eye. A good part of Nirenberg's life must be in those 40 volumes, so future scholars will probably have easier access to him than his contemporaries.

Nirenberg was born in New York in 1927. His father went to medical school for several years, but when he got married, he dropped out and joined the family business. Nirenberg's paternal grandfather came to the

Marshall Nirenberg with one of his numerous notebooks (photograph by I. Hargittai).

United States from Odessa, Russia, when he was 12 years old. He got a job in a shirt factory, where he slept on the floor; eventually, he owned the shirt factory and built it into a nationwide business. He had five sons and a daughter, and all the sons went into the shirt business.

Nirenberg's maternal grandparents came from somewhere in Poland. His mother was a university graduate. His father always regretted that he hadn't finished medical school, and he encouraged his son to study. Both of Nirenberg's parents died before he had visible success, but he'd told them about his work.

When Nirenberg was a child, he went to the synagogue on the High Holidays but he is not religious. After the genetic code was deciphered, he wondered whether the code was the same in *E. coli*, in amphibians, and in mammals. They prepared tRNA, they did all the experiments, and they found that the code was the same, that it was essentially a universal code. He was familiar with evolution and Darwin and understood them, but this was on a different level. When looking outside the window, seeing the trees and seeing the squirrels, and knowing that the genetic code of these organisms was the same, or essentially the same, as the genetic code in him, he found that a very powerful philosophical concept. It had a

profound effect on him, and he found an almost religious significance in this unity of Nature.

Nirenberg had had rheumatic fever from age 8 to 13. At that time, nobody knew what caused it, it was a big killer among children, and bed rest was all they could prescribe for him. At one time, he spent a whole year in bed. They also thought that a warm climate would be better for him, so his father decided to give up the shirt business and the family moved to Orlando, Florida. His father started a new business there.

Nirenberg has been interested in biology from early childhood. When he went to camp as a 6- or 8-year-old, he always won the nature award. Florida was still unspoiled when his family moved there. They lived on the outskirts of Orlando, which was a small town at that time, way before the arrival of Disney World. There was a tremendous swamp nearby that went on for 20 miles without a house in sight. Every afternoon, after school, he roamed the swamp. He collected spiders for the American Museum of Natural History.

Nirenberg was in high school during World War II. There was a big air base at Orlando, and professional biologists from all over the United States were brought in to teach a jungle survival course to pilots who were going to the South Pacific. One of them was an ornithologist, and Nirenberg was very much into identifying birds at the time. With two other boys, he went to talk with this ornithologist, Lieutenant Frank McAmey, who invited them on birding expeditions. On one such trip, they went to Merit's Island, later renamed Cape Canaveral, to see a rare bird called the dusky seaside sparrow, which is now extinct.

After receiving his B.S. degree in zoology and chemistry from the University of Florida, Nirenberg joined his father in a candy manufacturing business, but he did not like it and decided to go back to the University of Florida for another two years to earn his M.S. degree in zoology. Nirenberg had taught comparative anatomy as an undergraduate, and while he was in graduate school, he had a part-time job as a technician in the nutrition laboratory, working with radioactivity. This was his first exposure to biochemistry and he got hooked. Looking for a graduate school for doctoral studies in biochemistry, he wrote to three places, Wisconsin, Michigan, and Duke. He was accepted by all three, but Michigan offered him a fellowship to work in the lab and teach medical students. He enjoyed the years in Ann Arbor, where Jim Hogg was his mentor.

Nirenberg started working at the NIH right after his doctorate, on a postdoctoral fellowship. Upon its completion, he wrote to François Jacob

because he wanted to spend some time in Paris at the Pasteur Institute. Some of the most exciting work that came out of molecular biology in the 1950s was that carried out by Monod and Jacob at the Pasteur Institute, using a model system to study how genes were regulated. Their studies involved genetic experiments on *E. coli* bacteria. But nobody knew from a molecular point of view how genes were regulated. Nirenberg and his colleagues called these elegant and beautiful experiments the latest Parisian fashion. Alas, Jacob, apparently flooded by applications, did not take Nirenberg. Thus, Nirenberg never spent any considerable length of time away from the NIH. In 1961, Nirenberg married Perola Zaltzman. She is a biochemist, and although they never worked together, they discussed their work all the time.

To Nirenberg, in the late 1950s, protein synthesis was the hottest field in biochemistry. The best biochemists in the world were working on the biosynthesis of proteins. They had just discovered transfer RNA and the amino-acid-activating enzymes that catalyzed the activation of transfer RNA to link an amino acid to a particular species of transfer RNA. They also knew that proteins were synthesized on ribosome particles in the cells. But nobody knew anything about the messenger.

This was the first problem that Nirenberg worked on as an independent investigator at the NIH, where he stayed on after his postdoctoral fellowship. He asked himself, "What chance do I have as a single person against the best people with big groups in the best laboratories of the world who are working on protein synthesis?" He thought that within two years protein synthesis would be solved and then he would set up a protein synthesizing system and would study how to regulate gene expression by proteins in a cell-free system.

As he started his research, Nirenberg hypothesized that probably RNA was transcribed from DNA and that probably RNA was the template for protein synthesis. But he thought that protein synthesis could also come directly from DNA. So he tried both, and his first experiment worked. He realized that RNA was stimulating protein synthesis. From there on, he just had to improve the system. Heinrich Matthaei, a plant pathologist from Germany, was Nirenberg's first postdoctoral fellow. In 1960, Matthaei came to the NIH to work on protein synthesis, and at that time Nirenberg was the only person there who was working on protein synthesis. Nirenberg speaks about him with admiration and regrets that Matthaei decided not to stay at the NIH when his postdoctoral fellowship ended. Rather, he returned to Germany, got a large laboratory, and did a lot of work at

the Max Planck Institute in Göttingen until his retirement. In their joint project, they ran concentration curves of everything in the reaction to get the optimum conditions. First, they used ribosomal RNA and then viral RNA, which enhanced their efficiency by several orders of magnitude, and then they tried synthetic polynucleotides, synthetic RNAs.

Nirenberg had found that viral RNA was a tremendous stimulator of amino acid incorporation into a protein. Heinz Fraenkel-Conrat at Berkeley, a great authority on tobacco mosaic virus, had some mutants that Nirenberg thought were directing the synthesis of viral coat proteins. He went to Berkeley to work with Fraenkel-Conrat for a month, using viral RNA to direct protein synthesis. He packed a bag of enzyme-containing extracts in a picnic basket and brought it on the plane. This was at the beginning of 1961. Before he left, he wrote a whole series of protocols for Matthaei, using synthetic polynucleotides in a cell-free system, and Matthaei was actually the person who did the first poly(U) experiment. When this happened, he immediately called Nirenberg, who returned to Bethesda at once.

Nirenberg goes out of his way to stress that deciphering the code was a group project. Many people contributed to it at the NIH, like Maxine Singer and Leon Heppel and the postdoctoral fellows who came to work with him. When the book *The Eighth Day of Creation* comes up in conversation, Nirenberg calls it an awful book. He finds the description of how the code was deciphered terrible and thinks that the author, Horace Judson, didn't capture the atmosphere in the lab at that time in the book, although they had talked several times. Since Nirenberg does not elaborate on his criticism, I can only guess that he might have found the description of Matthaei's contribution exaggerated in the book. He stresses over and over that deciphering the code was teamwork. It took about six years, between 1961 and 1966. They worked as hard as they could, and he had about 20 postdocs on the project, at most 9 at any one time. The atmosphere in the lab was exhilarating, everything they touched worked, and discoveries were coming fast and furious. He compares it to walking into a toy store and seeing all the toys on the shelves and being able to pick whichever one they wanted to play with.

There was great excitement when they discovered that a sequence of U's in poly(U) is the RNA code word for phenylalanine. They then started to make randomly ordered polynucleotides with different bases, mixtures of bases, and so forth. They did not know the sequence, but they knew the base composition. Nirenberg was sure that it had to be a triplet code because there are four bases and a doublet code could only provide 16

Marshall Nirenberg in 1967 (courtesy of Marshall Nirenberg).

permutations, not enough for the 20 amino acids. It took about three years to determine the base compositions of codons for the 20 amino acids. Then they had to determine the base sequences. For this, they tried at least 10 different approaches. The approach that really worked well was a very simple one. He posed the following question: "What's the smallest message that we could detect?" They could indeed determine the sequence in each codon by simple experiments, allowing them to decipher the code between the nucleic acids and the proteins. Most of the trinucleotides had never been prepared before, and the major problem was to make the 64 triplets for testing.

As we neared the 1961 Moscow announcement of the discovery in our conversation, it was like approaching the crescendo in a musical movement. He knew that he really had a terrific thing to report at the meeting. However, being unknown in the field, in fact, in any field, he was assigned 10 minutes in a tiny room with a giant-size projector, and there was only a handful of people. He had introduced himself to James Watson before the talk, somewhere in a hallway, and told him what they had done. Watson sent a colleague, Arnold Tissières, to Nirenberg's talk, and he then corroborated what Nirenberg had told Watson. Word soon reached Francis Crick, who chaired a large session on nucleic acids at the Moscow meeting, and Crick

invited Nirenberg to give his talk again, at the same meeting, but this time to a much bigger audience. When Nirenberg gave the talk the second time, he was overwhelmed by the response.

This was indeed the first time that anybody had shown definitively in an *in vitro* system that RNA directs protein synthesis. It was obvious that they had identified the first codon. They had shown that polyuridylic acid, poly(U), directs the synthesis of polyphenylalanine, a protein. A series of U's in RNA corresponded to the amino acid phenylalanine. This was the beginning of the deciphering of the genetic code, the translation between the structure of nucleic acids and the structure of proteins. A synthetic RNA, containing only one kind of base out of four, when added to their cell-free protein synthesizing system, directed the synthesis of a protein consisting of only one kind of amino acid, out of the 20 amino acids. This is what they proved and this is what Nirenberg presented at the meeting.

As soon as Matthaei first reported to Nirenberg the results of his experiment, Nirenberg understood that this was a staggering discovery and that they had to be very convincing. He knew he had to "prove it upside, downside, and every which way." He wanted an unambiguous physical characterization of the polyphenylalanine product. They isolated it, demonstrated its stoichiometry, that all of it was incorporated into a product that precipitated in trichloroacetic acid like most proteins do.

If the discovery was serendipitous, proving the identity of the protein wasn't lacking serendipity either. Nirenberg wanted to find out something about the physical properties of polyphenylalanine. On his way to the library, he went by Christian Anfinsen's lab, which was just one flight below his. Anfinsen was an expert on protein structure and he was to win the Nobel Prize for his work on the structure of ribonuclease in 1972. Nirenberg didn't find him in the lab; instead, he found a young visitor, Michael Sela, who was spending his sabbatical with Anfinsen. He later became President of the Weizmann Institute. Sela was very knowledgeable about synthetic peptides and he used them in immunology. He told Nirenberg that polyphenylalanine was very insoluble, that it wasn't soluble in normal solvents, but it did dissolve in 15 percent hydrobromic acid dissolved in glacial acetic acid. Sela just happened to have this solvent at hand and offered a sample to Nirenberg.

Only about 20 year later did Nirenberg find out that Sela was the only person in the world who knew about that solvent. It so happened that Sela had once made a mistake when he was using polyphenylalanine as a reagent to study carboxy-terminal amino acids of proteins. Instead of doing his assay

in the right way, he poured a suspension of polyphenylalanine in the wrong solution, which was this particular combination, and polyphenylalanine dissolved to Sela's surprise. As it turned out, on his way to the library, Nirenberg asked the only person in the world who could answer his question.

The discovery that was the first step in deciphering the genetic code raises an interesting question with broader implications about scientific discovery. Here was a tremendously important question with enormous competition among the best laboratories in the world in looking for the answer, and a beginning scientist not only hits on such a seminal problem, on his own, but also finds the solution. However, Nirenberg hastens to point out that there was yet at least one other person dealing with the same question independently. It was Severo Ochoa, one of the world's leading biochemists, who had won the 1959 Nobel Prize in Physiology or Medicine for his discovery, with Marianne Grunberg-Manago, of polynucleotide phosphorylase. Apparently, Ochoa was on the right track but did not have the serendipity that helped Nirenberg and Matthaei so much.

For Nirenberg and Matthaei, the experiment with poly(U) proved to be lucky indeed. The sample was a gift from a colleague, Dan Bradley, at the NIH. Bradley was a physical chemist who studied the properties of nucleic acids. He synthesized poly(U), which would not have been available commercially at that time. Nirenberg remembers with gratitude that Leon Heppel, one of the few great experts in the world on nucleic acid chemistry, was also at the NIH and he was a tremendous help, and so were others. Heppel gave Nirenberg his first triplets, and he also gave him the idea of an enzymatic method to synthesize triplets, all 64 of them.

Another fortunate feature of Nirenberg's situation was that the NIH supported his research. He could do whatever he wanted to do, and he didn't have to write grant applications. The NIH didn't mind either that he went on without a paper for two years. Had he applied for a grant, chances are that he would have been turned down because of his complete lack of any experience related to what he would have been proposing to do. When he applied to attend a Cold Spring Harbor Symposium, prior to the Moscow meeting, he was turned down because he was unknown in the field.

Immediately before Nirenberg left for Moscow though, he had written two papers for the *Proceedings of the National Academy of Sciences (PNAS) of the U.S.A.* Since he was not a member of the Academy, Joseph Smadel, the Vice-director of the NIH, submitted them. However, when he later

asked Smadel to sponsor yet another of his papers in *PNAS*, Smadel said, "Nirenberg, I've done enough for you."

Nirenberg also tells about an experience with Leo Szilard in this connection. Szilard was a Member of the National Academy of Sciences and he was in Washington, so Nirenberg had asked him to sponsor his first papers in *PNAS*. When Nirenberg called him, Szilard invited him down to the Dupont Hotel, where Szilard lived at that time, on Dupont Circle. His office was the lobby of the Dupont Hotel. He was deeply involved in questions of defense, he knew all the people from the Pentagon and from official Washington. They would come to the hotel, and he would confer with them. So Nirenberg came, and since Szilard was a physicist, he asked Nirenberg to explain the work to him. Nirenberg spent the day talking to Szilard in the lobby of the Dupont Hotel, explaining to him what they'd done and what the implications were. People passing through kept interrupting them all the time. At the end, Szilard said, "It's too much out of my field. I'm sorry, I can't sponsor it." This was an unexpected ending to this charming story because Szilard was famous for his foresight and, at the time of their meeting, he had already been much involved in biology. This makes this encounter even more interesting. Nirenberg and Szilard later developed a cordial relationship and saw each other on numerous occasions when Szilard went to the NIH to learn about molecular biology.

It was upon completion of the deciphering of the genetic code but before the Nobel Prize that Nirenberg decided to change fields and go into neurobiology. He was attracted by the challenge and he was always interested in the nervous system. When about a year later he won the Nobel Prize, it did not change his life much because for him the continuity of work was the major determinant. He continues doing basic research to this day. He does not patent, never has.

His interest is in the development of the nervous system, and he speaks about his present work in neurobiology with enthusiasm. He finds the way the nervous system develops in *Drosophila* incredible. The homeobox genes have provided the opportunity to investigate the early events in the development of the nervous system. They encode proteins that bind to DNA and regulate gene expression. They turn genes on and they turn them off. Thomas Morgan found two of the homeobox genes in *Drosophila* 90 years ago. One is *Antennapedia*, which converts the antennae to a pair of legs, and the other is *Ultrabithorax*, which converts the fly with two

wings to a fly with four wings. These single mutations have become the favorite topics for genetic exploration.

Nirenberg and his associates discovered four homeobox genes in *Drosophila*. One of them turns on neural development in part of the central nervous system. It is called NK2. They were the first to clone it, but it was discovered genetically earlier and was called VND, the ventral nervous system defective. During evolution, the NK2 gene has been duplicated in mammals. In the mouse, there are seven copies of this gene that have different roles. Mutations in two of them have been studied. Knocking out one of these genes results in mouse embryos that lack the ventral part of the hypothalamus in the brain, their lungs are missing, and the thyroid is missing. When the other gene is knocked out, the ventricle of the heart doesn't develop. So at least one of the genes has a key role in the development of the brain and the central nervous system, and the other, in the development of the heart.

Nirenberg compares his laboratory of about 25 people to a university department. There are four independent investigators, each having a group. In his group, there are eight postdoctoral fellows and two technicians. One of them has been with him for decades.

The long afternoon is ending, but before we leave, Nirenberg patiently subjects himself to a photography session. He photocopies some hard-to-find papers for us and sees us off. After we bid each other good-bye, I see him walking back down the hallway. Soon, he will be sitting at his huge desk in his cluttered, windowless office, beginning slowly, comfortably, today's entry in his latest notebook.

Daniel Nathans, 1999 (photograph by I. Hargittai).

10

Daniel Nathans

Daniel Nathans (1928–1999) was University Professor of Molecular Biology and Genetics at The Johns Hopkins University School of Medicine in Baltimore, Maryland, and Senior Investigator at Howard Hughes Medical Institute. He received a B.S. degree in chemistry in 1950 from the University of Delaware and an M.D. from Washington University School of Medicine in St. Louis in 1954. He has been at Johns Hopkins University since 1962. In 1978, Dr. Nathans shared the Nobel Prize in Physiology or Medicine with Werner Arber and Hamilton O. Smith "for their discoveries concerning restriction enzymes and their application to problems of molecular genetics." He was a Member of the National Academy of Sciences of the United States and a recipient of the National Medal of Science. We recorded our conversation in Dr. Nathans's office at Johns Hopkins University on April 2, 1999. Dr. Nathans died in Baltimore on November 16, 1999.

I would like to ask you to summarize your Nobel Prize-winning research for us.

If you will permit me, I would first like to give you some background about myself and then reply to your question. I was trained as a physician. It had been my intention to practice medicine, or it's perhaps more accurate to say that it had been my father's intention that I practice medicine. However, after my first year at Washington University Medical School, I spent the summer in a research laboratory with Oliver Lowry, professor of pharmacology. It was a wonderful summer. The two of us worked side-by-side

at the bench. Ollie, as he liked to be called, was a wonderful human being and creative. That time with him completely changed my plans for the future. I decided that medical research at the biochemical level and teaching suited me better than medical practice. I thought that being an academic physician would be just right.

After a residency in medicine, in 1959, I went to the laboratory of Fritz Lipmann at The Rockefeller University to study protein biosynthesis, which I had gotten interested in through previous research on plasma cell tumors. Probably Lipmann's most important contribution to biochemistry was the recognition that ATP is the source of energy in almost all biosynthetic reactions. He published a review article in 1941 in which he discussed the high-energy phosphate bond of ATP and how it drives biosynthesis. In 1953, he and Hans Krebs shared a Nobel Prize.

When I arrived in the lab, Lipmann was intensely interested in the energetics of protein synthesis. That was before the notion of a messenger RNA that encoded proteins, and just after the discovery of aminoacyl-transfer-RNA (tRNA) as an intermediate in protein synthesis. Clearly, the transfer RNA was an informational molecule, which Francis Crick had predicted must exist to go from a nucleotide sequence code to an amino

Daniel Nathans in Fritz Lipmann's laboratory at The Rockefeller University in 1960 (courtesy of Daniel Nathans).

acid sequence code. Then came Nirenberg's finding that poly(U) directed the synthesis of polyphenylalanine in a bacterial extract, which led to solving the genetic code.

I worked initially on identifying soluble proteins that were involved in peptide-bond formation. Starting with aminoacyl-tRNAs and ribosomes, transfer of amino acids to growing peptide chains of proteins was dependent on adding soluble (nonribosomal) proteins and GTP. These soluble proteins were later called the transfer factors Tu and Ts. While in Lipmann's lab, I also collaborated with Amos Neidle at Columbia University to clarify the way puromycin inhibits protein synthesis and then with Norton Zinder, James Schwartz, and Gur Notani at the Rockefeller to show that the RNA of a bacterial virus serves as a messenger RNA to direct the synthesis of viral coat protein in bacterial extracts. The atmosphere in Lipmann's lab and at The Rockefeller University as a whole was intoxicating. I learned

Fritz Lipmann's (1899-1986) research group on the roof at The Rockefeller University in 1961 (courtesy of Daniel Nathans). Back row, l. to r.: S. Michelson, R. Monro, R. Wolfendon, G. Spyrides, P. Szafranski, F. Chapeville, G. von Ehrenstein, G. Zubay, T. Langan; middle row, l. to r.: B. Lane, C. Gillespie, W. Eisinger, S. Manz, F. Lipmann (Nobel Prize in Physiology or Medicine for 1953), E. Hasegawa, R. Traut, L. Spector; front row, l. to r.: T. P. Bennett, Y. Mano, J. Schwartz, D. Nathans, M. L. Barker, J. Goodfriend.

a great deal. In addition to the research itself, there were many stimulating visitors and colleagues to talk to. I decided to look for a position in a basic science department of a medical school rather than a clinical department as I had planned.

So, in 1962, I came to Johns Hopkins and joined the Department of Microbiology, where I continued to explore the mechanisms of protein synthesis directed by viral RNA. Soon my interest in viruses broadened, partly as a result of an assignment to lecture to medical students about animal viruses. This led particularly to an interest in viruses that cause cancer in animals and cell transformation to tumorigenicity in culture. Molecular understanding of these properties of tumor viruses seemed promising. There was already initial molecular characterization of the genome of one of the smallest tumor viruses — polyoma — by Renato Dulbecco and Jerome Winograd. I decided to learn more about tumor viruses and in 1969 took a six-month sabbatical leave to go to Leo Sachs's laboratory at the Weizmann Institute in Rehovot, Israel. There I met Ernest Winocour, who was involved in studying tumor viruses at the molecular level, and from him I learned how to handle the viruses. I became convinced that the thing to do was to work with the simplest virus that had the property I was interested in, namely, transformation of cells in culture to tumorigenicity. I settled on the polyoma-related simian virus 40 (SV40) because it was easy to propagate in tissue culture. SV40 is an icosahedral virus whose genome is a circular DNA duplex of about 5000 nucleotide pairs, enough information for just a few genes.

At this point, my interest in tumor viruses crossed with the interest of my colleague at Hopkins, Hamilton (Ham) Smith, in restriction enzymes. I had known about restriction and modification of viruses by bacteria and the work of Werner Arber and of Matthew Meselson and Robert Yuan on DNA restriction. In 1967, Smith discovered a restriction enzyme in *Hemophilus influenzae*. He then decided that the best thing he could do was to determine if the restriction enzyme cut DNA at a specific nucleotide sequence. He and Thomas Kelly showed that indeed it did; that is, there was a specific sequence at the ends of the cut DNA. Ham wrote to me about his progress in the sequencing while I was at the Weizmann Institute. It occurred to me that restriction enzymes were comparable to trypsins and chymotrypsins for DNA and would be valuable tools for analyzing the genome of viruses like SV40. One could produce pieces, maybe gene-size pieces, find out what the pieces do, create physical maps, and follow the

example of the proteolytic enzymes to chop up viral DNA into sequenceable pieces.

I began to read about restriction enzymes. At that time, probably four enzymes were known, including Ham Smith's enzyme. The other enzymes, derived from various strains of *E. coli*, were later classified as class I restriction enzymes. They require ATP and S-adenosylmethionine for DNA cleavage activity. Ham Smith's enzyme was smaller and required only magnesium. Enzymes of this type were later called class II restriction enzymes. As I was returning home, I laid out a series of experiments to see if any of these enzymes would cut SV40 DNA. I brought home a little DNA, and in the summer of 1969, Stuart Adler and I purified the *E. coli* enzymes and got the *Hemophilus* enzyme from Ham Smith. When we tested their activity against SV40 DNA, three of the enzymes cut the DNA. Two cut it once; they opened up the circle and made it into a full-length, linear molecule. The *Hemophilus* enzyme cut SV40 DNA several times. We were very excited because here we had a battery of enzymes with which we could start the physical mapping of the DNA. It turned out that class I restriction enzymes, although each binds to a specific sequence in DNA, move along the DNA before they cut, and they cut randomly. These enzymes were therefore unsuited for our purpose. However, Ham Smith's enzyme, the first of the class II restriction enzymes, each of which binds to a given nucleotide sequence and cuts either at that sequence or very close by, proved very useful. Kathleen Danna and I found that 11 specific fragments produced by the *H. influenzae* enzyme could be separated by electrophoresis in polyacrylamide gels.

Over the ensuing decade, my colleagues and I, notably Adler, Danna, George Sack, Ching-Ju Lai, William Brockman, Mary Gutai, and David Shortle, used restriction enzymes to construct a physical map of the SV40 genome based on the order of restriction fragments in the circular DNA; to excise predetermined segments of DNA to construct SV40 deletion mutants and later base substitution mutants; to map viral genes, the origin of replication of the DNA, and RNA transcripts; and to use "DNA fingerprinting" to distinguish one viral strain from another. The classical way of doing genetic analysis of viruses is to randomly mutagenize a virus stock and then select those phenotypes that you are interested in. By using restriction enzymes, one could start with the physical map and construct many of the mutants one wanted. And when methods for cloning DNA became available, the methods we used to analyze SV40 DNA could be applied to cloned cellular genes. It was an exciting time.

The Nobel citation stated that you'd found applications of the restriction enzymes in genetics. How do you look at this from a 20-year perspective?

I'm well aware that it's 20 years later now. Compared to today's state-of-the-art molecular genetics, our approaches were rudimentary. But they did, I think, contribute to such important advances as DNA sequencing, DNA cloning, DNA fingerprinting, and *in vitro* mutagenesis, as well as molecular genetics more generally.

Does DNA cloning pose any danger to humans?

The discussion of danger started with concern about putting genes into microbes, particularly bacteria like *E. coli* that can grow inside of us. If those bacteria got into the human body, what might that do in terms of causing disease? Now, 25 years later, I'm not aware of anything bad having happened, and much that is good.

What about "mad cow disease"?

That's a peculiar disease. It's thought that it's caused by an unusual form of a cellular protein, so-called prion. It doesn't appear to involve nucleic acid. Some way or another, which nobody understands, that protein gets into brain cells and, it's thought, nucleates a polymerization reaction leading to protein fibers that cause damage to those cells. It has nothing to do with cloning, except that cloning prion-related genes has provided a great deal of insight into the disease. If you are asking whether there is risk in producing prion-related proteins in the laboratory, I think that one does have to be cautious in our present state of understanding.

Wouldn't those proteins be created by nucleic acids?

Oh, yes. They are proteins that are encoded in the animal's own genome, and it's thought that an unusual conformational state and high local concentration of this protein is what nucleates the damaging fiber formation.

Conformational changes are the easiest to induce of all structural changes, so to me this sounds rather ominous.

I understand your argument, but prion-associated infectious diseases appear to be rare. It's not clear how often this conformational change occurs, although recent work suggests the possibility that other, more common diseases like Alzheimer's disease and Huntington's disease may be related to non-native

conformational states in endogenous proteins leading to fibers and consequent cell damage. Empirically, prion infectivity is much lower than that of a typical virus. In any case, something that is missing in the hypothesis that an infectious protein causes mad cow disease or scrapie is the isolation of pure protein and showing that pure protein causes the disease when injected into an animal. Nonetheless, the concept that non-native conformational states of proteins, whether infectious or not, can underlie degenerative diseases is both provocative and sobering.

How did the Nobel Prize change your life and what have you been engaged in recently?

I can't say that the prize did not change my life, but it didn't change it radically. One of the nicest things that happened is that my postdocs found it easier to get jobs. In one case, one of my postdoctoral fellows was turned down for a job before I got the prize, and after I got the prize, the same job was offered to him.

Did he take it?

He did. It's a crazy world. On the other side of the coin, my students and postdocs never treated me with the same directness as they used to. A Nobel laureate, I learned, is faced with a large number of petitions to sign. But there are many good causes in the world, and sometimes one likes to help, even if only a little. I was also recently asked to serve as interim president of this university, and I did that. I stopped being chairman of the department four years after I got the Nobel Prize and became a Senior Investigator of the Howard Hughes Medical Institute. I continued in research, although less and less with my own hands.

In the early 1980s, I decided that we knew quite a lot about SV40, the virus, but we didn't know very much about cells and how the cancerous process started. I got interested in looking for genes that were activated when cells were stimulated to grow and divide. That's what I've been spending my time on. I also became more involved in other activities, for example, with foundations and the National Academy of Sciences.

When were you elected to the Academy?

I was elected to the Academy in 1979, the year after I got the Nobel Prize.

Isn't that unusual?

It is. But it happens. The same thing happened with my colleague Ham Smith, and others as well. I later noticed that if nominated after receiving the prize, laureates are elected much faster.

You majored in chemistry and graduated in 1950. What turned you to chemistry originally and then what turned you away from it?

I was a premedical student. I didn't have the customary history that I was always interested in science and had a chemistry set. I didn't have any of that. I grew up during the Great Depression. My family was in trouble, my father lost his job. I come from a very large family. I'm the last child of eight children. I worked as a wage earner, you might say, from the time I was in the sixth grade up through my college years. I had lots of decent teachers during my early schooling, but nobody struck me as special except my elementary school music teacher. When I went to college, I was interested in a lot of things. I could've ended up being a literature major or philosophy major just as well as a science major. Several professors in liberal studies were excellent. However, it was my father's strong desire to have a physician in the family, which was never satisfied by his older children, and I was his last chance. The truth is I didn't have much insight into what other careers were possible. I had a broad education in college, I took a lot of advanced courses, and chemistry was strong at the University of Delaware. So it seemed like the best major for a premedical student. Also, my sister had been a chemistry major there before me. Considering my later interests, chemistry turned out to be a good choice.

Is Johns Hopkins one of the centers of biomedical research?

Yes, I think so, and it has a history. Hopkins Medical School was built a little over a century ago on a German model, where science became strong and full-time faculty staffed every department. Many medical schools in the U.S. were later organized like Hopkins. But perhaps your question is really aimed at the importance of not resting on your institution's past laurels.

Are you involved in biotechnology?

I've been a long-time consultant to the Monsanto Company and have had the interesting experience of witnessing the development of

their large and successful programs in agricultural and pharmaceutical biotechnology.

Do you patent your discoveries?

Had we done that, the School would've made a lot of money, but neither Ham Smith nor I were thinking in those terms in the early 1970s. It was Ham's discovery of the first useful restriction enzyme and my use of restriction enzymes that were potentially patentable, I believe, but neither of us was thinking along those lines at the time.

Would you be today?

Absolutely. It occurs to everybody now. I remember getting a call from one of our university officers involved in patents, saying, "Aren't restriction enzymes patentable?" and I said, "You are about 10 years too late."

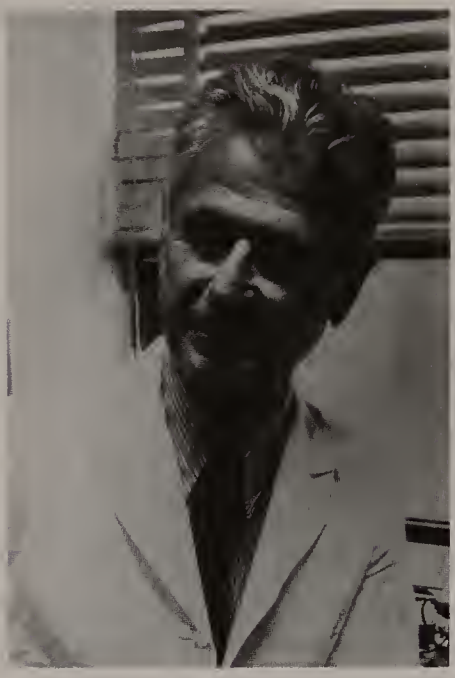
What do you like to do apart from science?

I read: history, memoirs, novels. I enjoy re-reading certain novels periodically, like *War and Peace* and *Pride and Prejudice.*

My children also help keep me intellectually alive. One of my sons, Ben, is a Russian historian. When he was working in the archives in St. Petersburg, my wife and I visited him for a few days. Another son, Eli, is a graduate student in German history. Jeremy, my middle son, is a molecular biologist and neuroscientist. He is in this department. He is his own person and self-confident. I wondered about the difficulties that might be caused not so much by his being in the same general field as I am, but by his coming to Hopkins. When he and I talked about it prior to his coming, he told me he could handle it, and he has. It's certainly enjoyable for me to have him so close by.

What does your wife do?

Until recently, she worked for the City of Baltimore, drafting legislation for the City Council. She has a background as a lawyer, but she has never practiced law. She remains involved in various voluntary activities in the city. She is now in a group that's analyzing employment problems among the indigent population of Baltimore to see what might be done to raise their skill level.



Oliver Lowry, about 1970
(courtesy of Daniel Nathans).

Among your teachers, who influenced you most?

Oliver Lowry's picture is up here; he was one of my teachers at Washington University in St. Louis. He probably had the most influence. He changed the direction of my career. Fritz Lipmann, here is a picture of him, had an important influence on me. Then Barry Wood, his picture is also here; he was Professor of Medicine at Washington University when I was a student. He then moved here to Hopkins and became Head of the Microbiology Department, and he hired me and was very supportive. I succeeded him as chairman of the department.

Who are your heroes?

They come in different categories. There are the distant ones: Abraham Lincoln, Churchill, De Gaulle, Einstein. But the ones that have meant the most to me are the ones that are closer by: two of my brothers, some of my teachers, some of my colleagues, including some younger colleagues, some of my students. It's always meant so much more to me what people are like as human beings than what they accomplish. Then there are some fictional characters among my heroes as well, Pierre Bezukhov in *War and Peace*, for example.

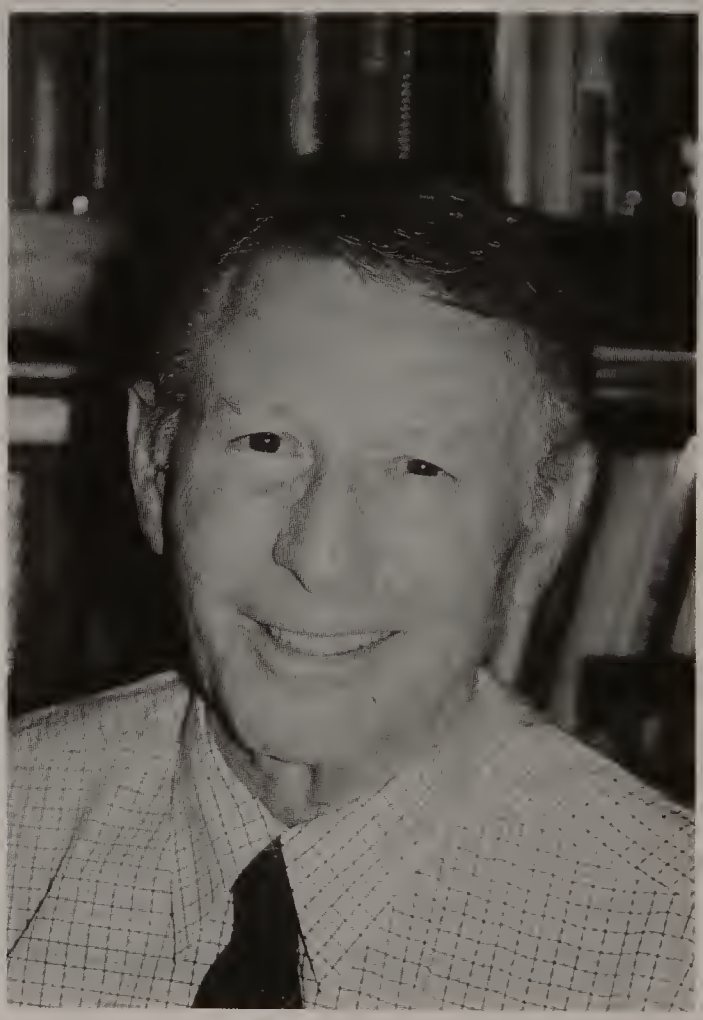
You mentioned that you like to read memoirs. Whose memoirs do you read?

Johns Hopkins University, Department of Microbiology, 1976, l. to r., Kenneth Berns, Thomas Kelly, Daniel Nathans, Hamilton Smith (Nobel Prize, shared with Daniel Nathans), Bernard Weiss (courtesy of Daniel Nathans).

Middle Europeans especially. My parents came from Russia, from the area around Vitebsk in Belorussia, and since my adult years I have had an interest in modern European history. My parents came here as teenagers to join older siblings who had preceded them. They were married in the U.S. My parents spoke Yiddish, but by the time I was growing up, English was spoken at home almost exclusively, and unfortunately I didn't learn Yiddish. Our family wasn't religious; in fact, a reason for my father's leaving home in his mid-teens was that his father was a strict Orthodox Jew. My father found life in early 20th century Russia outside the shtetl, and later in America, more exciting.

Did your parents witness your success?

My mother did. My father died when I was at The Rockefeller University. My mother was in a nursing home at the time of the Nobel Prize. She was frail, but she was absolutely clear mentally. My mother avoided bragging about her children. After the Nobel Prize was announced, people kept praising me to her, and my mother, who carried the feeling that pride was asking for the evil eye or bad luck for the family, replied simply, "I have other children, you know."



Paul Berg, 1999 (photograph by I. Hargittai).

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Paul Berg

Paul Berg (b. 1926 in New York City) is Cahill Professor in Cancer Research in the Department of Biochemistry and Director of the Beckman Center for Molecular and Genetic Medicine at Stanford University School of Medicine in Stanford, California. He was awarded the Nobel Prize in Chemistry in 1980 "for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA." This was a shared Nobel Prize, the other half being awarded jointly to Walter Gilbert and Frederick Sanger "for their contributions concerning the determination of base sequence in nucleic acids."

Paul Berg received his B.S. degree from Pennsylvania State University in 1948 and his Ph.D. from Western Reserve University in 1952. He did postdoctoral work at the Institute of Cytophysiology in Copenhagen and at Washington University in St. Louis. He joined the faculty at Washington University in 1955 and moved to Stanford University in 1959. Dr. Berg's honors include the Eli Lilly Award (1959), the Gairdner Foundation Award (1980), the Albert Lasker Medical Research Award (1980), the National Medal of Science, and the National Library of Medicine Medal (1986). He is a Member of the National Academy of Sciences of the United States, Foreign Member of the French Academy of Sciences, the Russian Academy of Sciences, and the Royal Society (London), and Member of the Pontifical Academy of Sciences. He has held numerous science policy appointments. He is a director of the biotechnology companies Affymetrix, Gilead Sciences, and Transgene.

Our conversation was recorded in Paul Berg's office at Stanford University on May 13, 1999.*

Can you pinpoint the beginning of your interest in science?

It has struck me how many scientists read the same books as kids. We read Paul de Kruif's book *Microbe Hunters* and Sinclair Lewis's *Arrowsmith.*

Did you know that de Kruif contributed the science-related parts to Arrowsmith? He writes about it in detail in a later book, The Sweeping Wind.

I learned something now. The young people today seem never to have learned of these books. They don't even know who Sinclair Lewis is. One year I gave a copy of *Microbe Hunters* to every student in my lab.

You originally went to City College of New York but then you left it.

I grew up and went to high school in Brooklyn. My parents did not have enough money to let me go away to university, which would have been very nice. But because my grades in high school were good, I was eligible to become a student at City College with free tuition. When I enrolled in City College, I had to take a bus, a streetcar, a subway, then a second subway to go there. It took 2 hours and 15 minutes one way. The system of registration for courses was very primitive; it took me three days to make my program. According to my program, I had to be there at 8 o'clock in the morning, then my next class was at 1 o'clock in the afternoon, so it was really crazy. Another thing was that the first class I went to was a physics class. It was a lab and they had a whole group of objects that you were supposed to measure then you performed statistical analysis on your measurements. I had never before seen the tools used for measuring. I came from a general high school. Many of the other students came from technical schools and they knew all the instruments, but I didn't know how to use them. So I asked the young man who was sitting next to me, and he looked at me like I was challenging him to a duel, as if saying, "Don't bother me." There was no instructor there. I had gone to City College to become a chemical engineer. I was

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interested in chemistry for reasons I can't remember. I thought that chemical engineering was what I would like to do. After three days, I decided that I did not want to be a chemical engineer and I went to another part of the City College system, which was called Brooklyn College. It was much closer to where I lived. I went there as a biology major. The first course in biology at that time, in 1943, was to cut open frogs to study animal anatomy; very boring, so I decided biology was not interesting for me. At the same time, a friend of mine that I'd grown up with had gone away to Pennsylvania State University. He was enjoying it and he sent me a copy of the catalog of all the courses they offered and I saw biochemistry among them. I had never heard of biochemistry before, but I thought it was interesting and I went away to Pennsylvania.

At that time, I had just turned 17 years old and I enlisted in the Navy to be a flyer. In that program you were first sent to a university to learn some basic sciences related to navigation, math and physics, and so on. So while I was in the Navy, I spent three terms studying biochemistry in addition to the required subjects. And I liked biochemistry because it had to do with chemical processes related to living things, which I'd always been interested in as a kid.

After the war, when I came back from the Navy I went back to Pennsylvania State University and I got my undergraduate degree in 1948. By that time, I knew I wanted to go for a Ph.D. The reason for this was that during the summers I worked for the Lipton Tea Company and for General Foods. I did analytical chemistry in the laboratory. When I looked around, there were people who were the leaders and they were telling other people what experiments to do. The leaders had Ph.D.'s and the ones who had to do the experiments had bachelor's degrees. I wanted to be the one who decides what experiment is to be done.

My expectation was that I would end up in a commercial company, probably in the pharmaceutical industry or in the food business. Both had a lot of biochemistry, which at Penn State was mainly analytical chemistry. But in my last year I read a group of papers that had to do with the use of isotopes. The war had ended, radioactive isotopes were available from Oak Ridge, and there was considerable research being done using radioactive molecules as tracers to study metabolic reactions. That group of papers came from Western Reserve University. It was startling what you could do with this new technique.

My mother and father were Jewish immigrants from Russia. They married back in a small shtetl outside of Minsk, and the next day they left and never saw the family again. They worked their way through Europe. It took them three years, ending when they sailed from Belgium to the United States. Their name was Bergsaltz but at U.S. immigration it was changed to Berg. At the time I was growing up, I never appreciated my parents' courage in doing what they did. When they arrived here, they had a baby who died not long after they came. Thus I was the second born but the oldest child. I have two brothers. Like other Jewish families, we lived among Jewish people in New York; some of them were people from the same village. My mother kept kosher but our family was not deeply religious. We went to Hebrew school. We spoke Yiddish at home and I didn't speak any English until I went to school.

Little Paul Berg (on the left) with his family (courtesy of Paul Berg).

There was a very strong tradition of learning even though my parents had no extensive schooling. My father left school to work and my mother never talked about her school; but for their kids to go to school and do well in school was mandatory. They also took great pride when we did well. They talked about it with their friends. My mother didn't live to see me get the Nobel Prize but my father did. He was then 80 and died at 85.

The kids I went to school with were largely of the same kind of background. In junior high school there were special classes for gifted people, and we took the 7th year and 8th year in one year. It was one of the most extraordinary groups of young people because we fed on each other, and the level of excitement of learning and the kinds of things we did that were not in the program of the regular classes made a very strong impression on me. It very much motivated me for science.

I had a very unusual experience in high school. They had a woman there, Sophie Wolfe, who supervised the school stockroom from which they brought out the microscopes and various demonstration things for all the science classes. It was her job to supply the various classes in chemistry, physics, and biology. She was not a teacher but she just loved the students

Paul Berg as high school student (courtesy of Paul Berg).

and started science clubs. You stayed after classes were over for the day and you worked in her laboratory. She never gave you an answer to a question but she always encouraged you to find out for yourself. Sometimes that meant doing an experiment, sometimes it meant going to the library, but it was always you who had to solve the problem. After my Nobel Prize, *The New York Times* ran a full-page article about her. It turns out that Arthur Kornberg and Jerome Karle, also Nobel laureates, went to the same high school and were also protégés of Sophie Wolfe's. Some years ago, the City of New York named one of the wings of this high school the Sophie Wolfe Wing.

While I was a Ph.D. student, I worked on a problem that at the time was a central concern in biochemistry. One of the most distinguished biochemists, Vincent du Vigneaud, who later received the Nobel Prize in Chemistry, had proposed that mammals cannot synthesize methionine, an amino acid needed for growth and survival. Instead, methionine must be made by transferring a methyl group intact to homocysteine, the methyl group being derived from what he called methyl donors — choline or betaine. My Ph.D. adviser had shown, however, that under certain conditions animals could synthesize methyl groups *de novo* from simple molecules like formaldehyde or formic acid. I took up that work and showed that it could occur *in vitro*. Thus, liver tissue had enzymes that could reduce formic acid or formaldehyde to a methyl group and attach it to homocysteine in the test tube. Later, we and others showed that this process required folic acid and Vitamin B12, substances that were missing from the diet of animals that du Vigneaud was using.

When I presented my work at a national meeting, du Vigneaud stood up and questioned me aggressively about my data, and I defended my conclusions just as aggressively. He seemed placated and later the chairman of my department told me that du Vigneaud contacted him asking if he could offer that young assistant professor in his department a position at Cornell University in New York. My chief told him that I was not a faculty member but a Ph.D. student! That apparently surprised du Vigneaud. After completing my Ph.D. thesis, I went to Copenhagen to spend a postdoctoral year at the University's Institute of Cytophysiology and then for the second year of my postdoctoral training to Washington University to work with Arthur Kornberg.

In 1952, Feodor Lynen and Fritz Lipmann, two of the most famous biochemists in our time, both future Nobel laureates, published a theory of how to explain a particular biochemical reaction central to a lot of metabolism.

I saw that paper while I was in Denmark and I was very excited about it. The model they proposed suggested for the first time that the substrate reacted with the enzyme and became a part of the protein structure through a covalent bond. They predicted a series of steps in which the substrate remained bound to the enzyme at each step. The first intermediate was a nucleotide bound to the protein. I thought it was conceivable that such complexes were involved in making nucleic acids because this linkage was an activated linkage with a potential to be transferred.

When I came to St. Louis, I told Arthur Kornberg that I wanted to work on that system. Kornberg said, "I don't believe a word of it." This was because he could explain the experimental results that led them to the hypothesis in another way, which was trivial. However, he let me work on it. I began to purify the system more than they had done and very quickly showed that their results were an artifact and that the reaction could be explained in a totally new way. This led to the hypothesis of a new kind of compound. I synthesized this compound, which had not been made before, and showed that it behaved in the reaction exactly as I had proposed. The word about what I had done spread among the people attending the annual Biochemical Society meeting, particularly that I had found a new kind of reaction that explained this whole system in a much more believable way. Lipmann and Lynen were at that meeting, and they asked me to present the new results, as I wasn't scheduled to give a talk, which I did. It was clear that I was right. Lynen came to me and confessed that he was embarrassed because he had never been shown to be wrong and he told me that I was the only one who had shown him to have made a mistake. It was clear that they had been sloppy by using a system that was dirty. There is an old saying in biochemistry, "Don't waste clean thoughts on dirty enzymes." I didn't suspect that Lipmann and Lynen were wrong. I thought they might be right and that's why I insisted on looking at the reaction. I wanted to isolate what they'd proposed, an enzyme-adenylic acid complex, because it was an interesting molecule and might donate adenylic acid to make nucleic acids. Kornberg believed their explanation was wrong because their evidence could have been explained in another way. He said, "They missed the point. That system would've given those results for another reason." So they had no reason to propose this new kind of compound. But I was persistent and I wanted to try to see. What I found was that the mechanism they proposed was totally wrong and it had to be another way, and the other way was quite obvious from the results we got with the purified enzyme.

The key was in the nature of the intermediate compound. This was a reaction that requires ATP and it produces pyrophosphates. We found that it reacts with acetic acid and the adenylic acid is joined to the acetate to make the new compound called acetyl adenylate, which nobody had seen before. This is the basic mechanism for activating fatty acids.

At the time this work was done, I was a postdoc of Kornberg. One of the remarkable things about it was that Kornberg, who by that time was a very big name in the field, let me publish all the work by myself. He did not put his name on the paper. Had he put his name on the paper, as was traditional, he would have received all the credit, and I would have been seen as a promising young student in his lab. As it was, right from the very beginning it was my discovery. I always remembered that it was an incredibly important happening because it provided national recognition. I was seen as someone who had upset this accepted view of how things happened from two leading biochemists. Now I was somebody whose name was known and I began to get all kinds of offers for jobs and so on and so forth, but I wanted to stay in this department at Washington University, which was a great place. When people ask me, of all the things that I've ever done in science, which do I have the most pride for, it is that discovery, not the one that got the Nobel Prize.

What made it so important? Your age, that is, that it was made at an early stage of your research career, or its scientific merit?

Scientific merit was one. Two, it was nonobvious. Making recombinant DNA was pretty obvious. All you had to do was to say, "I want to do it."

The discovery you just described, wasn't it a discovery almost by default? You did not set out to make this discovery.

That's right. I didn't set out to make this discovery but, again, if I look back, there was a pretty good guess of what the right answer was. You had to deal with a new compound that was not known before. You had to say, "If it's not this, what else could it be? How else could you explain the kind of data that you were getting?" I must admit that I was not what I would call an experienced chemist, but I actually synthesized this compound. When I synthesized it, it had all the properties that you would predict it would have. This discovery also did two things. It disproved

Paul Berg during the interview (photograph by I. Hargittai).

the Lipmann-Lynen hypothesis, and it opened the door for many other kinds of systems that have the same kind of reaction. For example, in making proteins we have to activate amino acids energetically so that they are able to join other amino acid molecules. This occurs by the same mechanism. ATP reacts with the amino acid to eliminate two phosphates and make the amino acid-AMP. A whole new world opened up by just doing this new kind of reaction. Looking back, it had an enormous impact, it was original, it wasn't obvious, and it was at a stage when I was just starting out. The Nobel work was more obvious.

Would you summarize it for us too?

I had been working with bacteria, and one of the powerful things in that work is doing genetics with bacteria. You could transfer genes from one bacterial cell to another, and you could do this in a variety of ways. One way, which was very powerful, was to take a virus and grow it in one cell; the virus would then pick up genes from that cell, and when the virus infected a second cell, it would bring those genes from the first cell into the second cell. So you could move genes from one cell into another, using viruses as the carrier. That proved to be a very powerful methodology for analyzing the function and regulation of genes. The process is called transduction. By 1965, we knew the basic way by which genes worked: they made messenger RNAs (mRNAs), the mRNAs were translated into

proteins, and we knew the genetic code. Also, we knew a good deal about what regulates whether a gene will or will not make mRNA, and how much. There are also inducers of mRNA production. Wally Gilbert was one of the key persons in discovering this regulatory system. Also, Jacques Monod and André Lwoff and François Jacob worked along these lines. The question in the mid-1960s was whether what we understood about the basic design of a simple genetic system like a bacterium was also true in a human cell. I decided in 1965–66 that I wanted to stop working in bacterial systems and to see if we could study gene expression in human cells or animal cells.

One of the most powerful tools for studying genetic expression in bacteria was to use viruses. The reason is that viruses have very small chromosomes. When they infect the cell, this little chromosome takes over the cell and uses the cell machinery to multiply itself, kill the cell, and produce a couple of thousand new virus particles, and so on. It occurred to me that one logical way to approach the mammalian cells was to use viruses that grow on mammalian cells.

I went away in 1967 and spent a year at the Salk Institute in La Jolla and worked with Renato Dulbecco. He was one of the major figures in the field, and at that time he had only recently discovered a new group of viruses called tumor viruses. These are viruses that, following infection of a cell, can change the cell from a normal cell into a cancer cell. If you inject these viruses into mice, they develop tumors. Rather than killing the cell, the virus converts it into a cancer cell. It was clear that it was virus genes that made the cell grow like a cancer cell. That's why they are called tumor viruses. That was an interesting thing about which you can begin to ask questions about how does all this happen. At this point, I decided I was going to change the whole direction of my research to work on that problem.

When I came back from the Salk Institute in 1968, we established a whole new kind of laboratory here. I dropped what I'd been doing, which had been extremely successful. I was certainly a leader in the field in which I was working at that time. But it seemed to me that that work was going to go on and on and on the same way, and the prudent thing was to ask some new questions.

I began to think about the idea that if we wanted to study mammalian cells, it would be nice to have a way of altering the genetic makeup of cells grown in culture. The question was, could these tumor viruses pick up genes from one mammalian cell and bring them to another? And the

answer was, they couldn't. Even if they could, there were many reasons why we could not have detected it.

The chromosome from these viruses consists of just a small ring DNA molecule. We asked if it was possible to just open up this ring molecule by cutting it at some point and "sew" in genes that we wanted to transfer to another cell. The concept was quite simple. I was going to use the virus as a carrier of whatever genes I wanted to attach to its chromosome. So we could use a gene from a cell or from a bacterium or from a virus and then sew that gene back into the virus chromosome and let the virus chromosome infect the cells. When such viruses convert cells into tumor cells, the viral DNA inserts itself into one of the cell's chromosomes. Once it does that, it behaves like an ordinary gene of that cell.

So we set out to make viral chromosomes with new genes inserted into them in a test tube. We have the virus, we extract the chromosome from the virus, and cut the little DNA ring open, and insert into it another piece of DNA. The question is, how do we attach the two together? How do we actually form a recombinant, as we called it? The answer is trivially simple. We know that if you have the two DNA single strands and they have the complementary bases, A, T, G, and C, two will form a base pair. You take this piece of DNA and you synthesize onto its end tails of, let's say, A. Then you take the other piece of DNA and you synthesize onto its end tails of T. When you mix them, the A's and T's pair, the two bases form a double-strand bridge, and the two molecules come together. All you have to do is fill in the gaps a little bit and seal it, and you've produced one molecule of which a part came from the animal virus that causes tumors and the other part comes from any other source. That was the first recombinant DNA that was ever made. The reason why I say it was trivially obvious is because there were already viruses that had these so-called sticky ends. We knew the principle that if we have sticky ends and the two sticky ends are complementary, the two molecules will come together spontaneously. A year later, it became obvious that you didn't have to chemically synthesize these tails because there are certain enzymes that leave sticky ends when they cut the DNA.

Restriction enzymes?

Exactly. The purpose in our experiment was to seek an answer to the question of whether a mammalian cell could recognize and use genes that

came from a bacterium, or were the systems for expressing genes totally different in these two kinds of systems. If we take genes from a bacterium or a virus and attach them to a molecule and they go into the animal cell, become integrated into the chromosome, do they work? If they do, then we could begin to attach any kind of gene we wanted and get it expressed. So instead of using a virus to carry genes, we make the recombinant in a test tube. Then we could attach any gene we wanted. The following year, it was discovered that small DNA rings that are present in bacteria, called plasmids, could be opened and DNA could be inserted into them. When these plasmids are put back into bacteria; then they multiply in the bacteria. The bacteria are perfectly happy, carrying genes from a human or a plant, or from an elephant or a fly. The whole genetic revolution is based on that principle, that is, that you can make recombinants in a test tube and can propagate them in living organisms, bacteria or mammalian cells.

With the corresponding changes in properties.

Yes. It is this principle that gave rise to the prospects of so-called gene therapy. Suppose we have an animal cell and it is unable to grow under a particular set of circumstances because it had a mutation. If I introduce a normal copy of that gene, the cell grows perfectly fine. You've cured the genetic disease of that cell. You can do this by introducing a bacterial gene into a human cell.

In your paper "From Enzyme Chemistry to Genetic Manipulation" ...

I described that transition.

But you concluded it with a warning in the form of a question, "Do such experiments cause a potential biohazard for man and his environment?" This was about 20 years ago in a volume dedicated to Severo Ochoa. Can we answer this question now, 20 years later?

Yes, we can.

Would you, please?

When we began to do these experiments, people worried about "Would we be making bacteria more infectious?" In other words, if I take a gene from a cancer virus and I put it into a bacterium and that bacterium

can live in your intestine, does that create a big risk that you'll develop intestinal cancer? We didn't know the answer. If you take genes from organisms that are not sensitive to certain antibiotics and you put them into other bacteria that are sensitive to the antibiotics, do you change them to become resistant to the antibiotics? And the answer to all those questions is yes. So at that point we said, "Wait a minute, perhaps we should stop doing these kinds of experiments and determine if there is a real hazard or risk in doing these kinds of experiments." We certainly did not want to send bacteria out into the environment that could infect people, cause cancer or whatever. At the time, however, we had no way to determine whether the risk was real or imaginary.

As soon as it became clear from these experiments that you could move genes to and from all kinds of organisms, people said, "Are we going to create some monsters?" I was asked by the National Academy of Sciences to convene a group that would give advice to the Academy of what to do with this new science. This small group published a letter in the journals *Science* and *Nature*, which became known as the "moratorium letter." The "moratorium letter" suggested that everybody around the world should stop doing these kinds of experiments until we could meet and determine whether they posed a risk or not. This letter had a profound effect all over the world, and every country issued it to all its scientists working in this field, "Stop doing these experiments." In that letter, we recommended that there be an international conference where the scientists working in this field would come together and try to arrive at a judgment about whether these experiments were risky.

As a result, a now very famous conference called the Asilomar Conference was held in 1975. Asilomar is a big conference center on the Monterey Peninsula near Carmel, about a hundred miles south from here. The conference brought together 150 people from all over the world — from Russia, China, Europe, and the United States — all people who wanted to use this technology of genetic manipulation. The purpose was to ask the question, is it safe? And if it's not safe, what can we do to reduce the risks so that we can do the research. At the conference, we decided that we didn't have enough information to determine whether it was really safe or not. What we could say was that there are some experiments for which there are almost zero risk, and here is a group of experiments for which there are possible risks, and another series of experiments for which we think there's serious risk. We recommended working out a set of instructions and guidelines which everybody would accept: these

kinds of experiments could be done in any laboratory, these kinds of experiments would be done only in special laboratories, and these kinds of experiments would be done in only the most secure laboratories. The guidelines essentially regulated research for about 12 years, and because they were not set up by legislation, they were only recommendations, they could be changed.

As we learned more and more and found out that experiments we were worried about were perfectly safe, we could move them from the high-risk category to the low-risk category. Today there's almost no restriction on the kinds of experiments and molecules that you can work on anywhere. The work was going slowly at the beginning because people had to build special laboratories for it, but as it became clear that it was safe, the work expanded and exploded. Today I am quite confident that there is no risk to any of the kinds of experiments that we have been doing over the last 20 years.

Is there any relationship to the so-called mad cow disease?

No. The mad cow disease occurs in people who are eating materials from animals that have a kind of brain disorder, caused by a protein molecule, not a virus. This protein molecule is unusual because it can reproduce itself. Proteins usually don't reproduce themselves. Genes do. This protein is unusual in that it can enter into somebody's brain and can convert the normal form of that protein in that person's brain into an abnormal form, which causes the brain to disintegrate.

In what ways do the "normal" and "abnormal" proteins differ?

Structure. As far as we know, the normal form of the protein appears to have mostly α-helices. What happens is that the abnormal form changes its conformation and has less α-helix and more of parallel sheets.

So the composition is the same.

The composition is exactly the same.

When you say conformational change, this is usually the type of structural change that occurs most easily.

That's right. However, the probability that the protein would shift from one conformation to another conformation is near zero. On the other

hand, if you make mutations in the protein, the barrier to that switch changes, and the switch may be occurring with some probability.

Would the mutation mean a change in composition?

It would mean a change in composition. The spontaneous form of the disease happens when there is a mutation and the gene that specifies that protein changes the composition by, say, one amino acid. That one amino acid change increases the probability that the protein would switch from one conformation to the abnormal conformation. On the other hand, if you bring in the abnormal conformation, it induces the normal protein to undergo a switch from the normal to the abnormal, and it gets progressive.

The abnormal protein is called prion; it's a protein that has already switched. Its composition is the same as the normal one, but it has already undergone the switch of the conformation. Once it has switched, it induces normal molecules to switch. So the cow eats something that had the prion in it, and over time that protein gets into the brain of the animal and begins the slow process of switching the other protein molecules. It can take years.

Have the structures been determined?

The overall conformations, yes, but the proteins have not been crystallized and determined, and no studies have been done yet in the test tube. What has been done was isolation of the abnormal form of the protein from the brain; the normal form is available from the gene, and they looked at the two and they are different. But the amino acid compositions are identical. But nobody has mixed the two forms and observed the switch in a test tube. So that is inferred. And that's what the prion Nobel Prize was for.

The reference you mentioned to the Ochoa book was in the mid-1970s. At that time there was a lot of confusion and debate. Congress was passing laws, and other countries had all kinds of regulations. In Holland, for instance, scientists could not use genetic engineering tools. Many scientists left their countries. Japan was very slow in accepting that you could do it because there was this fear that genetic engineering meant creating monsters. Now all of that fear is gone. Now what we have is that in Europe people won't eat genetically engineered food. In this country, we have genetically engineered corn, genetically engineered rice. You can

put genes that protect the corn plant from pests that normally destroy the plant. So you make an antibiotic in the plant that protects it against its pests.

Do you have any reservations about genetically engineered food?

None, whatsoever. When you think about it, corn itself is a highly engineered plant. Over centuries, people have transformed what was almost a weed into an edible plant. Now you can do this in a much more directed way and in a much more informed way.

You have so far mentioned two areas of your research, one that you found most interesting and the other for which you received the Nobel Prize. Would you care to single out one more example, from the last 20 years?

I've been working on the process called genetic recombination. Genetic engineering is also referred to as recombination, but that is done outside the cell. The question is how do DNA molecules exchange parts in cells. There are two kinds of phenomena. We know that cells that form the sperm and the egg have two sets of chromosomes, two chromosomes for each gene, one from the individual's mother and one from the father. When such cells make sperm and egg, the genes that are on these two chromosomes undergo a complete exchange. The sperm and the egg contain chromosomes that are not like either one of two but are a composite of the two. Your sperm contains a composite of genes, i.e., new gene combinations, which were made at the time the sperm is made. The same holds for the egg. With each generation, we get a complete mixing up of the genes on the two different chromosomes. The question is, "What's the nature of that process?" It's a very simple process. The two DNA helices in the chromosomes are broken and the parts are exchanged. This process, the exchanges of homologous chromosomes, occurs by breaking the DNAs and then rejoining them. That's where the name recombinant comes from. The exchanges occur in all the 23 pairs of chromosomes. The only chromosome that doesn't exchange is the male chromosome. That's why you can use the Y chromosome to trace lineage of the male line so you can go back to the first man. This is why they could show that Jefferson's Y chromosome could end up in the male descendants of a colored slave. The other genes are more

difficult to trace. The Y chromosome can change only by mutations, not by exchanges.

The second thing that cells are able to do is repair broken chromosomes. If you irradiate a cell with X-rays, you cause the DNA molecules to break, which is usually a lethal event. But cells have an incredible capacity to repair these kinds of breaks. You irradiate with X-rays, and the cell rejoins the ends. They have several different ways of doing this. Either the two broken ends are stuck back together or there is a process of copying from another chromosome what's missing and then rejoining the pieces. We have been studying these ways of repair for the last 20 years. What is the mechanism of repairing of double-strand breaks in DNA and how does that relate to this process of recombination during this special process of producing the germ cells?

We've been identifying the proteins, the enzymes, and the genes that are responsible for being able to repair the DNA. We have incredibly efficient ways in our genetic makeup to repair all kinds of damage: ultraviolet light damages DNA, preventing that DNA from being copied. Our cells have very complicated machinery, which recognizes the damage, cuts out little pieces of DNA where the damage is, and resynthesizes and replaces it.

There are children who cannot go out into the sunlight because if they do, the ultraviolet rays produce melanomas on their skin. They live either completely covered up or inside using candles for light. Any ultraviolet light on their skin will cause damage to their DNA, and invariably the damage will initiate a tumor. If we didn't have this repair mechanism, we would constantly be generating cancers. The people who can't repair DNA damage are very prone to cancer. The genes that have been identified to cause early breast cancer in women are genes that are involved in repairing breaks in DNA. The process is very complicated, but the take-home message is the following. We have evolved to be able to protect ourselves against all kinds of damage of our genes. Sometimes the repair process doesn't work and the end result is that you have a mutation. If the mutation is in the sperm or in the egg, the mutation is passed into the next generation. If it occurs in the liver, it can cause a tumor in the liver.

Can this be repaired by science?

If we know that there are five genes that are needed to make the five proteins that carry out the process of repair and suppose that an individual

has a mutation in one of them, the DNA can't be repaired. If we could introduce the gene that's missing, then we'd cured the disease. The question is, "Can we introduce this gene in every cell of the body?" The answer is no.

If the disease is confined in one organ, for example, let's suppose that an individual has a mutation that doesn't allow him to make normal lymphocytes. The lymphocytes are born from cells that are in the bone marrow. If we could introduce the normal gene into the cells that live in the bone marrow and give rise to lymphocytes, then I could cure the disease.

Would you just introduce the genes or would you replace the bone marrow?

That's the debate. If you do bone marrow transplants, you have the problem of rejection. You will probably have to give drugs that prevent rejection and so on. There is a big debate. I happen to believe that bone marrow transplants are better than gene transplants, but many people believe that for certain kinds of disease it is better to bring in the normal kinds of genes.

Can behavior be changed by replacing genes?

Possibly, but not in the foreseeable future. First of all, behavior is a very complex phenomenon. Most likely, many genes contribute to a pattern of behavior. We don't know, but it may be 5, 8, 10 genes. If in fact certain behavior stems from the interactions of 10 genes, there is no way at present to be able to change those 10 genes.

As I understand, the relationship between genes and behavior is being mapped.

Yes. It turns out that some behavioral traits stem from overproduction of a chemical. After all, look at what drug addiction does to your behavior. It's induced by the fact that a chemical comes in and acts on various cells in the brain to produce a complex readout if you will. We don't know how many genes are involved in such a behavioral change. What we now know, because these experiments are going on, is that you can knock out one gene in a mouse and the mouse will fail to learn; can't learn, can't remember. In any kind of a training program, it will act as a stupid mouse. Another mutation can make the mouse a genius. It

learns how to do the trick that you want it to learn in one try whereas a normal mouse learns it in five to eight tries. All you've changed is one gene.

This points to a close relationship between genes and intelligence.

I don't know anybody who denies that. But it depends on how you define intelligence.

Isn't this almost a taboo question?

No, the experiments I mentioned are not concerned with humans. We're merely trying to understand what memory is. In what form is memory stored in our brains. Why do even very old people who don't remember what they did five minutes ago, remember the most minute details of various events from their youth? One way to learn about this is to ask if we can disrupt long-term memory. I will teach you how to do something and then I'll challenge you a month later. If you remember then what you had learned, that's long-term memory. But if you cannot learn, and I know what gene I had changed, I can say at least that that has something to do with the transformation from short-term to long-term memory. That's what people are trying to do. It turns out that the predominant paradigm in biology today in studying any complex phenomenon — it could be metabolism, it could be memory, it could be differentiation, it could be anything that you would like to understand — is to make mutations that affect that process. Once you have collected all kinds of mutations that alter the process, then the challenge is to study what each mutation is doing and reconstruct all the steps that are responsible for this complex process. For example, certain mutant flies can't learn, or they change their behavior to light. Any kind of phenomenon that you want to study can be studied by making mutations.

Is there a one-to-one correspondence, or are there other changes too that people may neglect to follow? You make something live longer but become also stupid or genius.

That's a good question.

Seymour Benzer is mapping the genes for behavior.

I just wanted to mention him. He's making mutations in flies.

George Beadle
(courtesy of Paul Berg).

He is using the same technique to study behavioral genetics that Ed Lewis used to study morphology.

Exactly, except that Ed Lewis didn't isolate the genes. He made mutations and he mapped them. Ed Lewis said, "Mutations affect development and morphology." If Seymour Benzer would follow Ed Lewis, he would say, "I'm going to isolate the gene that is responsible for putting legs onto the hand instead of antennas." And people are doing that. People are also looking for better and better systems and are now working with zebra fish. They make mutations in zebra fish, and they study development. It's what we call genetic dissection, and it goes way, way, way back to studies in the 1940s by a man I am writing a book about, George Beadle. He was one of the great geneticists who invented this technique for making mutations.

Would then the next step be to study these genes and mutations at the molecular level?

Absolutely. First of all, the molecular composition but, more important, what kinds of molecules do the genes specify, what kind of proteins do these code, and what do these proteins do, in what processes do they function. The long-term goal is to be able to say that we can explain what every gene and the human genome does in terms of the physiology, behavior, predisposition to disease, everything. That's a big job.

The first part of the job is to solve the genome sequence. Then we'll know all the genes. We won't know what the genes do; we won't know how they interact with each other to produce such a complex system. That's for the next hundred years.

For young people who are starting out, the game begins when the genome project is finished. When the genome project is finished, it's not the end of the game. The game starts because then we know the dictionary and now we have to find out what each word means, and how they relate to each other.

Do you wish you were starting out now?

Yes, for more reasons than that. First of all, there is a lot of excitement there, and, secondly, physically I would feel much better than now.

How did you decide to write a book about Beadle?

I was disappointed by how few young people even heard of de Kruif's book *Microbe Hunters* and of Sinclair Lewis's *Arrowsmith.* I was even more disturbed that they didn't know about people that I consider the heroes of the field, the people who made biochemistry and molecular biology into what it is. I decided to give a graduate course in which the students read original papers on how the genetic code was discovered. You have to go back to the beginning of the century to the rediscovery of Mendel in 1900. That was when people were beginning to see that there was a hereditary influence to certain diseases. There was an English physician who recognized that certain diseases clustered in families. His name was Archibald Garrod. Then the famous geneticist Thomas Morgan began to study flies. He was the one who first used *Drosophila* as an experimental tool for genetics, and he began to identify mutants. Normally, the flies have red eyes. He found a fly with white eyes, and he began to mate the white-eyed flies with red-eyed flies and he could show that Mendel was right; the genes were transmitted to the offspring exactly the way Mendel said they were in peas. They made more and more mutations, they got orange eyes, yellow eyes, and so on. Each one of them was a result of a specific mutation, which behaved like a Mendel factor. This went on and on and on, and people developed a whole scheme that the genes are on chromosomes, they are arranged like beads on a string, on the fly's four chromosomes.

However, young people coming along always ask the next question, "What is it we don't know? How do we explain this?" The good people ask those kinds of questions. If there's no explanation, they usually try to figure out some smart way to go. Beadle was one of these kinds of people. He came to Morgan's lab and he said, "We know that things develop from a fertilized egg, and then they produce larvae and the larvae become pupae and the pupae become flies. It's a very complicated process. Is this controlled by genes?" There was no answer. Morgan couldn't give an answer, and nobody could give an answer. So Beadle said, "I'm going to devote the next couple of years of my life to determining whether genes control development." He started to do some experiments and he got some very interesting results, which led him to believe that every gene specifies a single protein. Then a trait is nothing more than the end result of the functioning of those proteins. He was here at Stanford and was working right over in the main quadrangle in the basement. He worked also with *Neurospora*, which is a mould you find on bread if it has been around for long. He showed that the mould could grow on a simple culture medium of sugar, some nitrogen, some metals, and salt, that's all. The mould could make from simple materials in the medium everything it needed to grow: all the nucleic acids, the proteins. Then he took the *Drosophila* and he made mutants. Now he found that there were mutants that could not grow on that simple medium, but they would grow if you gave them a rich medium, which had all the things they could possibly need. So what is it that they can't make that they need? They've lost the ability to make something. By adding back one thing at a time to this culture, he could find out what makes this grow. You take different mutants, one at a time, and find out for each the specific material whose absence prevents its growth. Thus, Beadle began to realize that every mutation was controlling the ability to make something; that certain enzyme reactions were blocked. So he began to show that, for example, four different mutants blocked the production of the same end product. Then he showed that one mutant knocked out enzyme one, another enzyme two, yet another mutant knocked out enzyme three, and the fourth mutant knocked out enzyme four. The process consisted of four steps. Each mutant was knocking out one protein, either by making one that didn't work or by not making it at all.

That's where the paradigm started. You could dissect all of the biochemical pathways by making mutants that block the ability of making an end

product. That approach has grown and it gets into behavior, into development, into every possible thing you are trying to understand. The paradigm is get a mutant that can't do what you are studying and find out what that mutant is affecting. In principle, you could say that Seymour Benzer is going to isolate a bunch of mutants that all live five times longer than the normal one but they're all different mutants. You clone each gene, find out what each gene makes, characterize the protein, and then try to figure out how the five proteins affect the aging process. That's the logic.

Beadle was a very unusual man. He came from a very humble background, a very small farm in Nebraska. His mother died when he was a young boy. The book tracks genetics as it developed in this century. Beadle bridges the transition from classical genetics, à la Morgan, to molecular genetics because he made the connection between the gene and the molecule. He is a very pivotal figure because from his work the genetic control of proteins indicates that there has to be a code. If the gene specifies a protein, how does the nucleic acid, the DNA molecule, make a protein? The sequence of the gene must carry a message. The relationship between the gene and the protein, the genetic code, got worked out long after Beadle. It turned out to be three bases in a row specify one amino acid, a different set of three for each of the different amino acids; that is the message. If you read a gene from one end to another, and you own the genetic dictionary, you can deduce the protein it encodes. Working out the genetic code turned out to be very simple but the concept that there was a code was what was important. The concept came from a number of people, but once you knew that a gene specifies a protein, right away you could say that the structure of the gene must specify the protein. The only difference from one gene to another is the sequence.

So Nirenberg's discovery ...

It came much later ...

... should have been anticipated.

It was anticipated. What wasn't anticipated was what is the code. Up till then, theoreticians were speculating. Francis Crick laid down the general rules for what the code had to be. Sydney Brenner was another of the theoreticians. What was the dictionary? Nobody knew. Nobody knew how to solve it. The only thing that could be done was to isolate a gene and

isolate the protein that it specifies, do the sequence of this gene, do the sequence of the protein, and find the correspondence. That was like a whole life's work at that time.

Nirenberg's discovery, which electrified the world, was not a mistake in experimenting, it was a control. He was trying to isolate natural messenger RNA and translate it into a protein in a test tube. And he was getting tiny indications that that might be happening. He wanted to do a control. He said, "The messenger is clearly going to be the whole message of the gene, I'm going to put in a stupid kind of message, it has only one base, just one base. He puts in poly(U), and lo and behold it made polyphenylalanine. He went to Moscow and announced this result. Everybody realized immediately that if you could make synthetic molecules that would act like a messenger, then the code is done. There was then a bizarre period when people were making random sequences to try to figure this out. Gobind Khorana said, "I'm going to synthesize a message in which I know the sequence and then I look at the protein I make." That finished it. From 1961, when Nirenberg made his announcement in Moscow, to 1963–64, the code was done.

In the development of the code, the interesting part was not only how we solved the code. The interesting question was, and that's what I wanted my students to read about, what were the great ideas that actually led you to the idea that DNA contained a code. So they read all the original papers from 1902, and Beadle came up to be one of the heroes. As I said earlier, he decided to take a year off to see if he could set up an experimental system to study both genetics and embryology in the same organism. He went to Paris to join a man named Boris Ephrussi who had also been a postdoctoral fellow in Morgan's lab. Like most postdoctoral fellows, they spent the night in the lab and they talked and they dreamed.

So Beadle left his wife and child in Pasadena, where he was then, and went to Paris. He arrived there in June of 1935, and he and Ephrussi submitted a paper in November of 1935, which described an all-new technology for transplanting tissues from one fly to another. They analyzed 35 different kinds of mutations to show that several of the mutations must by specifying proteins that form a pathway to making the pigment in the eye. Five months and they came up with a monumental piece of work. Today's students would spend four or five years on such a project. Beadle came back and had 20 job offers from the best places.

The newlywed Bergs
(courtesy of Paul Berg).

At Caltech, Beadle built up one of the best departments of molecular biology in the world. After he left there, he became president of the University of Chicago. After he retired, he went back to doing science, to work on one of the major problems of corn genetics, investigating the origins of modern-day corn. He did a brilliant piece of work, which incorporated archeology and anthropology, in Central America and found that corn had originated from a plant called teosinte. Teosinte has seeds which pop when put into a fire. That became popcorn. He reasoned that the Indians who experienced this then selected better and better plants by standard breeding. Beadle showed that teosinte's chromosomes are very similar to that of the modern corn. Even at age 70, Beadle was doing creative science. Then he developed Alzheimer's disease and the last few years of his life he lived in a home in Southern California largely unaware of what was going on around him.

Please tell us about your present family.

My wife is a homemaker. She was a registered nurse, and she kept working while I was a graduate student and while I was a postdoc and while I was an assistant professor. She stopped when we moved here. We have one son, he does computer graphics, animation, totally different from what I do.

You have spent 15 years as Director of the Beckman Center at Stanford University. Would you care to say something about your experience?

I'm very proud of what we have done. This is a very unusual research center. It's not an institute in the traditional sense. I don't direct anything here. My plan was to build a center where we could bring together people who would interact and bring modern molecular biology and genetics to medicine. The whole idea was to recruit people of different backgrounds and organize them so that they would talk and interact with each other. Usually, basic scientists don't talk to doctors. Doctors don't understand the language of the basic scientists, and the basic scientists don't understand disease. We began recruiting people who were trained in medicine as doctors but did basic science. They act as the bridge. The top floor is biochemistry, the next is developmental biology, then comes molecular and genetic medicine, where we have this interface, and the bottom floor is molecular and cell physiology. Each of them is autonomous. My job is to figure out how to get people to talk to each other, collaborate, and educate each other. We've managed to do that. It is one of the top places in the world in our field. I feel very good about it.

Do you patent your results?

Never.

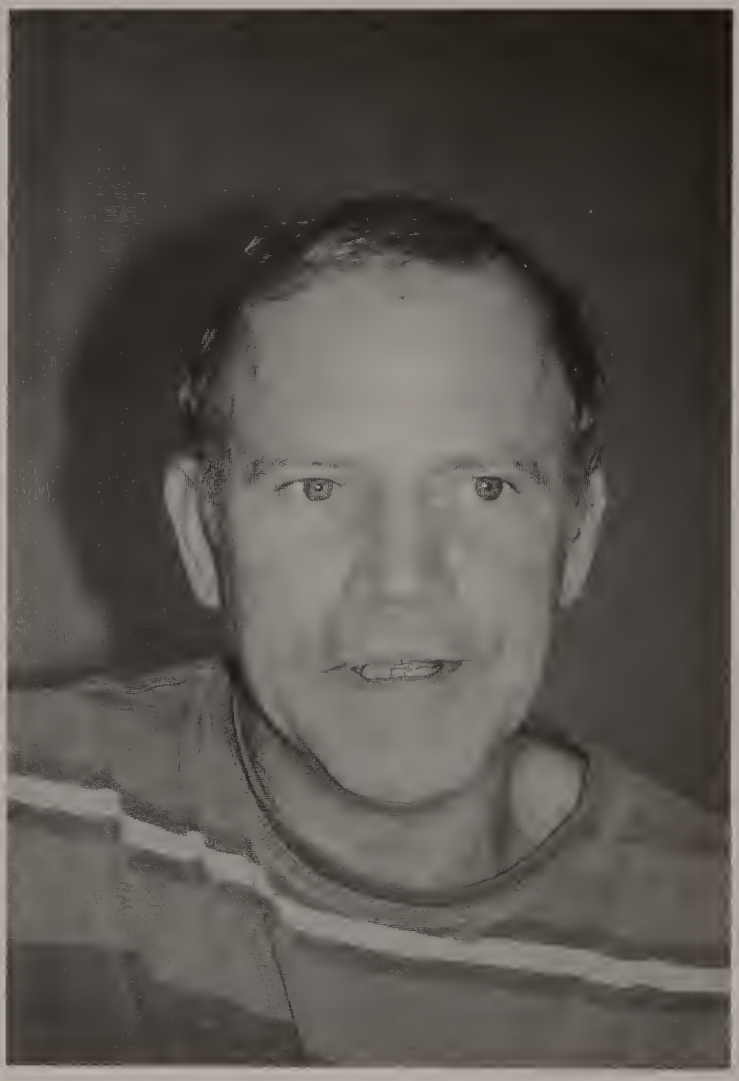
Are you involved in biotechnology?

For many years I didn't want to do that and I didn't, but in about 1981, I began to see that there was some value in setting up companies. They can bridge the university to the commercial sector, which is novel, different. We set up one company, which is a research institute serving a pharmaceutical company, which is 3000 miles away. The other one was based on an invention called DNA chips. You can put down DNA molecules on glass and use them to monitor a variety of genetic processes. In this way, one can look at 40,000 genes simultaneously in one experiment. They are like silicon chips except they have DNA molecules instead of transistors.

You have had a rich career and have done a lot of different things. If you could choose, what would you like to be remembered most?

I don't think I have a choice because it's already set. People call me the "father of genetic engineering." I'm not the father, because so many people

were involved, and in the area of genetic engineering what we did is light the first spark, and it changed the way everybody was thinking. We began to make new kinds of combinations in the test tube; we didn't have to rely any more on cells to do all this genetic manipulation. Once you had that, the genius of everybody out there made it into a big thing.



Kary B. Mullis, 1997 (photograph by I. Hargittai).

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Kary B. Mullis

Kary B. Mullis (b. 1944 in Lenoir, North Carolina) received the Nobel Prize in Chemistry in 1993 for the discovery of the polymerase chain reaction (PCR). This was preceded by the Japan Prize, which he won also in 1993. Kary Mullis graduated from the Georgia Institute of Technology, majoring in chemistry. He received his Ph.D. in Biochemistry from the University of California at Berkeley in 1973. We recorded a long conversation on November 4, 1997, at the home of Kary and Nancy Mullis in La Jolla, California. The following excerpts* from our conversation are mostly on topics that are not or are less elaborated in his autobiographical book *Dancing Naked in the Mind Field* (Pantheon Books, New York, 1998).

In writing about Erwin Schrödinger's book What Is Life?, *you, said, "I was living in Columbia, South Carolina, where no one noticed that we didn't have a copy." To me this is a very subtle way of describing your background.*

I came from a middle-class family. I recognized only later that some people had had parents who had lots of learned books around and my parents didn't. But both my mother and my father were very smart even though they were from the mountains of North Carolina. They had no idea where they had come from until I started figuring it out.

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My ancestors have been Americans for many generations. On my father's side they had come from a small village in Southern Switzerland called Flums. There are about 200 Mullises in that village. Otherwise this is not a common name. The mayor of Flums sent me a letter after the Nobel Prize, and one of these days I'll go there for a visit. But when I was a child, we didn't have this upper-class attitude of knowing where your family had come from.

My mother wanted us all to go to college and she worked very hard. I have three brothers and we all went to college. The Nobel Prize was announced on my mother's birthday, October 13. She was with me in Stockholm. She understood what it was but she still doesn't think that she should turn to me when she has questions about medicine. She still thinks that I am a kid and she is an adult. My two boys also went to Stockholm but my daughter couldn't because of her job. The boys' mother, Cynthia, was also there but Jennifer wasn't although she was my muse for the polymerase chain reaction (PCR) discovery.

You have made this comment about regretting that only a few people could understand what you had discovered and were awarded the Nobel Prize for.

This is because we work in a rarefied atmosphere of a very specialized field. Very few people know, for example, in this apartment building, what I do. They don't even know what subject it was in, yet everybody knows that I did get the Nobel Prize.

Nobody in the world doesn't understand the weight of the Nobel Prize. Once you have it, there is not a single office in the world that you can't go into. If I call them and say, I would like to talk to you about something, and I'm so-and-so, the Nobel laureate, they'll see me at least once. It opens every door. They also can't take it away.

I know that not everybody feels that way, at least they wouldn't tell you they do. Richard Feynman said that it was a burden. I liked him a lot though. Of all the scientists in this century, he is the one that I felt a strong bond to. Once I had moved to Southern California, I could've met him anytime, and I told myself many times that I should talk to him about physics. Then one morning on the radio I heard that he had died of cancer. I missed my opportunity.

I have a very long-standing interest in the stuff that he knew about so well. I had thought about becoming a physicist but then decided not

to. I knew that as soon as the Russians and the Americans decided that they were not at war with each other, or one of us was overcoming the other, they won't need as many physicists as they used to, and this is exactly what happened. Murray Gell-Mann told me that I was right. When I was at Berkeley as a graduate student in biochemistry, I was oscillating back and forth between physics and biochemistry. I thought it was a good idea to go into biochemistry because politicians are always getting heart attacks, and they die of cancer, so they'll need us. But they won't care what's falling out of the sky and they sure don't care how old the universe is. But I was young and I did.

My first academic paper, which I published by myself, was in *Nature*. I was still a graduate student in biochemistry, but it was about the deep secrets of the universe. I called it "The Cosmological Significance of Time Reversal" [*Nature* **1968**, *218*, 663–664] and suggested therein that there was a significant component of the universe, perhaps half of it, going backward in time. My logic offered an explanation for an earlier enigmatic finding, also published in *Nature*, by an Englishman named F. R. Stannard [*Nature* **1966**, *211*, 693], regarding the unexpectedly long half-life of the neutral kaon. The article got a lot of attention. Reprint requests poured into the department, and there was an article by the *Nature Times News Service*, which appeared in newspapers around the world, probably because of the catchy title, and the use of plain language when possible. It helped get me through preliminary examinations in the biochemistry department despite my having never taken any courses in molecular biology. At the time, and still today, it was a big deal to have a publication in *Nature*. For a graduate student to have published there without any collaboration in a field, which was not his, was something of a novelty. I have continued my interest in physics, cosmology, and so on, but more or less as a hobby.

It always bothers me how to reconcile the big bang and the steady state. I like the steady state in an aesthetic sense. They had discovered this four-kelvin background radiation and took it to be as a consequence and, hence, as proof of the big bang. To me, to think that that weak little thing you are measuring is really what you think it is, is like pushing your luck because it could also be something else. I didn't think there was good evidence for the big bang and I preferred the steady state. It was pretty philosophical thinking for a 24-year-old, but this is when you do your deepest philosophical thinking. The universe didn't happen, it is. If you start talking about when it started, then you're not talking about

the universe, you're talking about a subset of the universe that began in the universe at some point.

What made you turn originally to chemistry?

Rocket fuels. When I was about 13, I invented a solid rocket fuel, and I don't know how I did that. I heated a mixture of sugar and potassium nitrate in a 40–60 percent ratio by weight. I would go to the drugstore and buy a pound of potassium nitrate and would go to the hardware store and buy a hundred feet of dynamite fuse, no questions asked. Today this would be impossible, but this was 1957–1958. I made a rocket, four feet tall, of aluminum pipe, and there was a nozzle made out of asbestos, impregnated in plaster of Paris to hold it together. I put a tiny frog inside an aluminum film canister in the top of my rocket. I got the rocket two miles high and brought back the frog alive. This was by about 1960 or 1961 and we were excited by the Russian Sputniks. The first Sputnik went up in 1957, and Gagarin's flight was in 1961. My mother was interested in satellites. She would be watching them in the cold night. She gave me my first chemistry set.

After I graduated from Georgia Tech as a chemist, I worked in the nuclear reactor on the campus, just for the summer, for some lady who was a biochemist. My work was easy and not very interesting. We were working on methods for analyzing the allantoin content, the breakdown product of purine metabolism, in mammals, but not in humans. I set up cute little experiments, out of tubes that would go together, and pumps, building an automated system. It was like an erector set, and I had great fun with it. This work left me a lot of time to read. She had a three-foot stack of *Scientific American* and also *Science Journal,* which was a similar British magazine. I read them all during that summer.

How would you summarize the DNA polymerase chain reaction (PCR)?

At one point PCR was a fairly simple thing to summarize; it had to do with something I could see that other people couldn't, although a lot of people got very close. Now it is no longer possible to summarize it because it has led to so many things. I can't summarize my 20-year-old boy either.

DNA has this remarkable property that there are two forms of any particular sequence of the purine and pyrimidine bases that you can string together. If you can make one chain, then you can make another chain

that goes backwards in sequence; it is the complement, and the two chains are held very tightly. It's a beautiful helix but it is not perfect, it has kinks causing a lot of excitement. However, the two helices are clamped so tightly that you have to boil DNA to get them apart. This can also be done by an enzyme, burning a lot of ATP in the process.

DNA can reproduce itself. Clay can also do something like that, if you consider its layered structure, each layer being the complementary layer to the previous one. DNA has this ability.

If you make a short piece of one string of a DNA, like 20 bases, this piece will have a tremendous affinity for the complementary sequence. You put this 20-base-long sequence in a mixture that has a trillion (10^{12}) different pieces, and it will find the sequence that is exactly complementary to it in about 30 seconds.

Do you know how it happens?

Fast. DNA probably has some process of sliding on other DNAs. If you grind up DNA, it will take longer to find its complementary sequences than it takes for long pieces of DNA. The process is certainly less random than three-dimensional diffusion, it has got to do with surfaces, and it is convenient to think of it as sliding.

What PCR means is that that 20-base sequence finds not just one counterpart but it finds two in a coordinated manner. If there is a 10^{-6} probability of finding something at random and there are 10^{12} bases and I'm trying to distinguish them all, then it will mean $10^{-6} \times 10^{12} = 1{,}000{,}000$ hits. However, if I stipulate that the same sequence must be found twice, the probability will be $10^{-6} \times 10^{-6} = 10^{-12}$, and out of 10^{12} possibilities, there will only be one single hit. The PCR process requires that both ends be identified. Thus, something will be amplified only if both oligonucleotides find their counterparts. You put in two oligonucleotides, each of them having a high probability, relative to the number of bases in the sample, of making a mistake but a very low probability of making the same mistake twice. This is the beauty of it. People use now micromolar amounts and there are a whole lot of places that the oligonucleotide can bind and get extended by an enzyme that copies the rest of the DNA. You can get a very clean reaction.

I'm talking about a very practical thing. I can detect one viral sequence in the presence of 10 microliters of human blood in spite of all other DNA there. In a way you can say that I came to the PCR idea from

the rear. The PCR is an amplifier. At every step I can increase the efficiency, and the only task remaining is separation. PCR is a tool not just to find a rare thing but to use it for construction, making molecular biologists capable of moving things from one place to another, and sticking one sequence to another, stitching one molecule to another. I didn't think of this the first night when I invented PCR, it took me two more days to come to it. There used to be techniques for doing this before, but they were tedious and long. PCR does it in one tube in one hour.

Was it easy to publish your invention?

First I sent my paper to *Nature* because of the success of my sophomoric attempt about cosmology. John Maddox was again the editor, as he was for my 1968 paper. I never met Maddox until a symposium in 1993, although I was riding with him in the same elevator once but he was with some other big guy. Maddox was a real gentleman with the 24-year-old I was at that time. But he rejected my PCR paper, and *Science* also rejected it.

Weren't you afraid that others might come to the same idea and you would then lose priority in publishing it?

I talked to a lot of people about it and nobody ever believed what I was saying. Everybody was trying to explain me why it would not work.

You describe in your Nobel lecture that you came to the idea of PCR during a night drive from Berkeley to Mendocino on Highway 128. Under these circumstances, of course, you could not know whether somebody else had described it before in the literature.

I came back after I had thought of it and looked up every paper, and the searching techniques were not quite as good as they are now. It was 1983. I looked up every paper that had DNA polymerase in its title. There were lots of such papers and I couldn't find any that would come close to what I was proposing.

Are you familiar with Arthur Kornberg's book, The Golden Helix *[University Science Books, 1995]? There is a brief chapter about you in it with a photo.*

I don't know about this book but I would like to read it.

Did you find Kornberg's papers on DNA polymerase in your literature search?

I found lots of his papers. He never claimed that he had invented PCR. He claimed that Gobind Khorana at MIT had invented it and then had forgotten about it. [H. Gobind Khorana shared the Nobel Prize in Physiology or Medicine with Robert W. Holley and Marshall W. Nirenberg in 1968 "for their discoveries concerning the interpretation of the genetic code and its function in protein synthesis."]

Did you find Khorana's paper?

Khorana contributed heavily to the various uses of DNA polymerase. He and Nirenberg solved the genetic code. He also had a lab of a hundred postdocs. He's a prodigious guy. I saw him once. He was in the same hall at MIT as Leonard Lerman, a very scholarly molecular biologist. When suddenly DuPont decided that I had not invented PCR but Khorana had invented it, and DuPont went to court with that, I happened to be in Cambridge, Massachusetts. I went to see Lerman and asked him what is going on and he suggested that we go and see Khorana down the hall. I was sure Khorana wouldn't say that he had invented PCR and then forgot it.

By then, however, I had got involved with lawyers and I called my lawyer in San Francisco and told him that I might be able to clear up the whole thing directly with Khorana. But the lawyer said, don't go, don't talk to him. That's the way lawyers are. They saw two or three million dollars coming to them on this case. They didn't want to resolve it without the court.

Cetus hired me as an expert witness for the trial, and I had the privilege that very few scientists would have of going back in the literature, for 20 years back, and going through it paper by paper, and looking for details. They didn't have gels in 1969 to put DNA on. The analytical methods were inadequate. I learned everything they knew 20 years back, and I had the advantage of hindsight. They were close. There was one guy who probably would have come to it, except Khorana himself might have said, it won't work, but this is something I'm piecing together. They didn't know something what I found out in my experiments, that the relaxation time was very short, shorter than I could measure.

Did you find these papers in 1983 when you were checking the literature?

No, I didn't find these papers then. In 1983, my search specified DNA polymerase in the title. On the way back from Mendocino, I thought that if my idea had worked for somebody else before me, I'd know about that. So I wasn't looking for what had worked but why wouldn't it work, what didn't work? I would fix it and would make it work.

When did your paper finally appear?

Norman Arnheim's paper appeared in December 1985 in *Science* and my paper was published two years later as a chapter in *Methods in Enzymology* [Mullis, K. B.; Faloona, F. A. "Specific Synthesis of DNA in Vitro via a Polymerase-Catalyzed Chain Reaction," *Methods Enzymol.* **1987**, *155*, 335–350].

Was there ever any doubt that you were the sole discoverer?

The prettiest part of the whole PCR story is that when DuPont challenged the fact that I had invented it, in the courts, Cetus had to spend a couple of million dollars to show to the whole world that I had invented it. I was the only person on the patent.

When I got the patent finished, I was almost done with it, my boss at Cetus decided he wanted to be on the patent. I said, no, he wasn't even there when I invented it. My boss could get away with writing the paper about it but not with getting onto the patent because the federal law says that it is the inventor and nobody else who should be on the patent. You don't put people onto the patent because they are your boss. The patent attorney of Cetus knew that I was the person who invented PCR because the first person I ever told about my invention when it worked was this patent attorney, Al Halluein. He happened to be there in the night of December 16, 1983, when I got it to work. I was so happy, and there was nobody else in the lab. Only he was around, and I had to tell someone that it worked, and it was him. Al was a southerner and he was a friend of mine and he recognized at once that it was going to be the most interesting thing he has ever patented, and he said, "Congratulations!".

It took us about a year to write that patent, and Cetus wouldn't allow my boss to be on the patent. They knew they had better be careful with people who lay golden eggs for them. But the management people were creepy to me. They had come from academia to industrial science. I didn't like those guys and I didn't play poker with them.

You were not an insider.

No, I was not an insider. I'm not a company guy.

Is there any domain of society where you are an insider?

Yes, the intellectuals. Smart people like me and I like them.

Does it include academia?

No, I couldn't live there. I'm a little too feisty or sloppy for that. I don't toe the line ever. If it isn't sensible, I'm not going to do that even though it may cost me that I have to leave. It eventually became impossible for me to stay at Cetus. After I had invented PCR, I felt I should be at least allowed a certain amount of latitude.

Did you gain financially from PCR?

No. They gave me $10,000, but they didn't give me freedom. Instead, they gave me supervisors. There was a committee of five people and I had to meet with them every six months and they were going to tell me whether or not I had done well in the previous six months. These were people who had never done anything themselves.

Do you think you'll ever make another discovery of this magnitude?

I already have, I just keep it a secret. But, seriously, right now I'm working on something big.

Did you realize from the beginning that PCR was the discovery of such an importance as it is now?

From the very beginning I thought that it would spread all over the world. The very night I invented it, and I was trying to wake up Jennifer, I thought so. She was a biochemist and she was the only person that night who probably could've helped me. I wanted her to tell me why my invention wouldn't work, but she didn't wake up. The same night I thought that if it worked, I would get the Nobel Prize, and some day I would walk into the biochemistry department of the University of Zambia, they would know who I am, and they would ask me to say something nice to their graduate students. But I also had this doubt because it was so simple, why hadn't somebody else come up with it before? It took a lot of wine

that night for me to get to sleep. Then I woke up next day and I still couldn't find any reason why it shouldn't work.

It's true, molecular biologists should have or at least might have invented PCR before me, but it's also true that molecular biologists don't understand chemistry. They wanted to be doctors, for example. It's a crude thing to say, but molecular biologists are not very interested in chemistry. They wish that life was based on something else.

Would you care to say something about your company, Stargene?

We still have it, but it hasn't taken off yet. We were going to sell copies of DNA fragments of famous people, Elvis Prestley, Marilyn Monroe, Michael Jackson, Jerry Garcia, anybody, and package them. We got close to President Lincoln. We found a hair collection of all the famous people so you could make DNA out of the hair and with PCR you could copy as much of it as you like. For example, Michael Jordan's DNA could be built into basketball shoes, so people would buy them and jump higher. Just a gimmick. Like a pet rock. It didn't work because we didn't have any experience in licensing, for instance. It's waiting for its time.

How about the application in criminology?

They use it all the time. I get involved occasionally. There are still problems and I'd really like to fix them. Just take the O. J. Simpson trial. They took one sample of DNA from O. J. They put the sample in their crime laboratory. They did not take four more samples of just regular people. They had no idea about blind testing. Had they done that, they would have been far more convincing when they finally said, this was the guy. Worse than that, they brought O. J.'s blood into the same lab where they were processing evidence samples. It could have gotten into the air. It was totally ridiculous. You should be treating everything like infectious disease in such cases. The defense asked me to come up and testify in the trial, but everything had got discredited before I even would've had a chance to say anything.

I'm discussing this in detail in my forthcoming book, *Dancing Naked in the Mind Field,* which will be published next year. I'm not very cynical generally. I've always been wide-eyed, bushy-tailed, accepting whatever is there until it proved to be no good. This is what the title is referring to.

Kary and Nancy Mullis in 2000 (photograph by Magdolna Hargittai).

What are you doing now?

I'm employed half-time by a company called Vyrex. We are renting this apartment here in La Jolla. The other half time I'm up in Mendocino, where I was driving the night of the PCR discovery and where I own a house. Up there, I read and think and write. My wife, Nancy, my better half, does most of the interaction with the world for me.

Are you an eccentric?

I wouldn't think so.

Are you different?

Different, yes, although I'm not trying to be. I'm really not interested in what people think of me, but I know I'm a decent person, more decent than most.

You regretted that you didn't get to know Richard Feynman when he was still alive. Is there anybody whom you would like to get to know today really well?

Francis Crick lives here up the hill. He is not afraid of talking about topics that are completely out of his venue. The same way as I foolishly didn't get to know Richard Feynman, I haven't gotten to know Francis Crick real well although we have met a few times. I should be going

Kary Mullis making a point during the interview (photograph by I. Hargittai).

up there about once a month, I should be going up there tonight. But I don't. I don't have time. Maybe because of this conversation I will do that.

What did you do with the Nobel Prize?

As Yogi Berra, who had also won a substantial prize, said, I spent most of it on women and alcohol, and the rest of it, I wasted.

Somewhere you made a statement that the Nobel Prize should be delivered by royal messengers rather than having the Nobel ceremonies?

I probably said that right after the ceremonies. It was the most exhausting affair of my life for two weeks. I came back dead but I loved it. Even though I was dead by the end of it, I was still putting it out, performing the way I thought they were expecting me to. The most charming episode of the whole time I was there happened as I was leaving. I was taking a little boat from Malmö to Copenhagen. As I was getting on that boat, there was no fanfare associated with it, but somebody recognized me on the boat. He had a big hat and a big feather on it, a weird-looking Swede. He saw me coming on and he took off his hat and he bowed very deeply and he said, Dr. Mullis, the Swedish people love you. He said it real loud, and the people clapped, and I started crying.

Suppose a young person comes up to you today, say, from the Carolinas and asks for your advice, what would it be?

If a person is thinking about being a scientist, I tell him or her, if you can't help it and you have to be one, do it. You'll enjoy it. But if there is anything else that you can do, do that. We have enough scientists and it's not a kind of a career most people think it is. You are not going to get the Nobel Prize, and it's very unlikely that you'll ever be all that much rewarded for what you do. However, if you love it and you can't stand doing anything else, do it.

Like I couldn't stand not to be a scientist. I would just be helpless if I wouldn't know how to figure out stuff. If I run across a big white spill on the road and didn't know how to figure out that it's not dangerous, it would be a scary place, if you didn't know science. The world is so much ruled by technical things. If you don't know a little science, you don't understand technology. I don't mean to understand it exactly, but at least it gives you a feeling where the world of the 20th century is headed. I think politics will follow technology. A lot of people are cut off from their planet, they see the results of it, they have this feeling that somebody out there knows how this works. I at least know that nobody really understands how it all works. I know a little piece, you know a little piece, but nobody knows how to make a car from nothing, or a computer from nothing, or even a simple steam iron from nothing. It's a wild place that we live in. Knowing that I am a part of it makes me not afraid of it. It's a wild thing to say this on tape but I'm the most widely educated person I know of. Science, history, music, and so on. I've just been curious as hell all my life, and I was just doing things whether I could do them or not. I know that I don't know anything at all, but I know a lot more than most people. I still don't know how the world works, but I'm not afraid of it!

Gerald M. Edelman, 1998 (photograph by I. Hargittai).

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Gerald M. Edelman

Gerald M. Edelman (b. 1929 in New York) is President of Neurosciences Research Foundation and Director of The Neurosciences Institute and Chairman of the Department of Neurobiology at The Scripps Research Institute in La Jolla, California. He was co-recipient of the Nobel Prize in Physiology or Medicine for 1972 (with Rodney Robert Porter, for their discoveries concerning "the chemical structure of antibodies"). He earned his B.S. degree at Ursinus College in 1950, his MD at the University of Pennsylvania in 1954, and his Ph.D. at The Rockefeller Institute in 1960.

Dr. Edelman is a Member of the National Academy of Sciences of the United States, the American Academy of Arts and Sciences, the American Philosophical Society, and many other learned societies, and a Foreign Member of the Academy of Sciences, Institute of France. He has received numerous awards and honorary doctorates.

Our conversation took place during the Frontiers in Biomedical Science meeting in Indian Wells, California, February 1–2, 1998.*

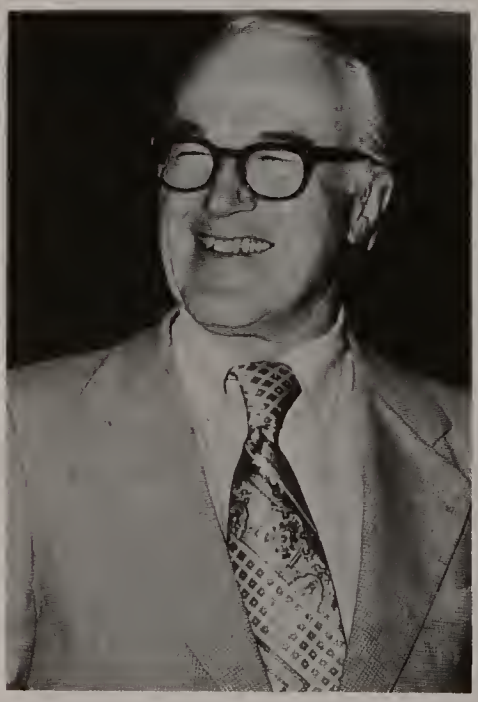
How did you go into science?

I was really interested in music and I trained to be a concert violinist. I had a teacher from St. Petersburg who was in the same class as Jascha

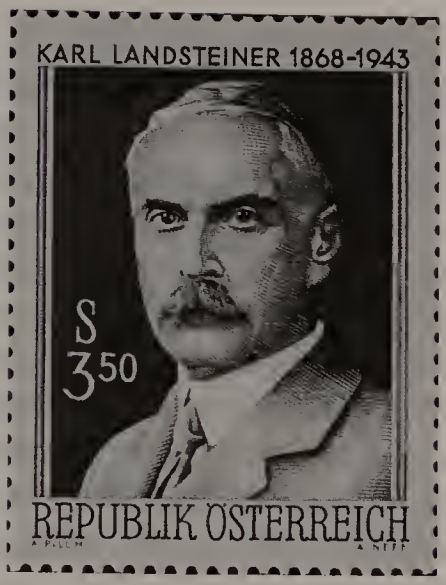
*Gerald Edelman's response to my first question was originally published in *The Chemical Intelligencer* **1999**, *5*(3), 18–23 © 1998, Springer-Verlag, New York, Inc.

Heifetz. I went so far that I started to concertize. My mother felt that this was wonderful if you were an amateur, but not if you were a professional. Her arguments were summed up in two words: "Jascha Heifetz." I didn't agree with her at the time, but by the age of 20 I realized that while I was a very well trained musician, I was not a performer. But I didn't want to go into an orchestra and I didn't have the talent for composition.

I had a rough time deciding what to do, and I finally chose science. Since my father was a doctor, I thought that in order to do research, I had to become a doctor. I went to medical school at the University of Pennsylvania. During my last year, I did some research with Britton Chance on fast spectrophotometry of enzyme reactions. Then I went on to Harvard and the Massachusetts General Hospital to get training in internal medicine. Although I never intended to practice medicine, I did this for a sense of completion. In the middle of that training, I was called by the U.S. Army, and went to serve in Paris as a general physician and surgeon to the Headquarters of European Command. It was lucky that I spoke French. I also served at the American Hospital in Paris to deliver babies and help in surgery; it was general medicine of the old-fashioned kind. In the middle of all of that I got a letter from my professor of medicine at Harvard, Dr. Walter Bauer, about a new university at The Rockefeller Institute, and in 1957 I became a Ph.D. student with an MD My area was the physical chemistry of macromolecules.



Britton Chance
(courtesy of Edit Ernster).



Karl Landsteiner (1868–1943) on an Austrian stamp.

The Rockefeller Institute was very special. It gave me a lot of freedom. I decided to work on aspects of immunology. While in Paris, I read a book on immunochemistry, and it was all about antigens, the foreign molecules that incite the immune response. However, there was practically nothing about antibodies. I had already read the great book by Landsteiner, *The Specificity of Serological Reactions.* So I came to New York from Paris with the idea of working with antibodies. Antibody molecules looked like footballs in textbooks, with no chemical structure. I was totally naïve about their size and what it meant in terms of chemical analysis, but I was not completely naïve about the problem of separation. Separation and purification are among the most important things in chemistry.

I was assigned to a laboratory and to a man who was not even a chemist. He was a medical man and a serologist. The first thing that attracted me was the notion of getting some aspects of the structure of the antibody molecule using ultracentrifugation. But first I devised a rotating amperometric electrode to measure thiol (SH) groups after reducing disulfide bonds. It was thought that the molecule I was investigating was a very long polypeptide chain. I planned to correlate the sedimentation coefficient from ultracentrifugation with the number of disulfide bonds I had cleaved.

There I came upon my first big discovery which, of course, I didn't realize at that time. Naïveté is often very important when you are young as long as you are knowledgeable. Another thing that is important is to find a contradiction in the literature that you can take seriously. What seemed to happen was that the antibody molecules slowed down in the centrifugal field to such an extent that it was impossible to explain it by the opening

of the chain and an increase in the frictional coefficient. I tried everything. The question was, how could this molecule slow down if it didn't have smaller fundamental units that were linked by disulfide bonds? At that time this was heresy. The major figure of the field, the man who was to receive the Nobel Prize together with me, but who was much older than I was, was Rodney Porter of London. He had already put out a very influential paper, which stated that there was one long chain. But he had the bad fortune to measure exactly one residue of alanine per mole of immunoglobulin molecule as N-terminal, and he concluded that this was consistent with the notion of a single chain. I came along, out of nowhere, and did this trick, which was absolutely incompatible with his findings, no matter how you looked at it. Except, of course, I was deeply challenged by the community for a variety of reasons. First of all, I was working with a three-component system, using urea, water, and protein. The theory of centrifugation was not as secure for three-component systems as for simpler systems; some people said it could be the binding of the urea molecules; others said that the problem was with the virial coefficients. For a year and a half, I went through a magnificently elaborate set of controls. I did 196 experiments too many. I already had the answer, but being challenged, I had to go through additional endless measurements and calculations. I was informed that I would not be received very well if I published this in a biological journal. I became exasperated and in 1959, I decided to send a Letter to the Editor of the *Journal of the American Chemical Society.*[1] For biologists, this journal was outside of the pale. That Letter was one page. It just said, Dear Sir, Reduction of the immunoglobulin molecule by such and so, ...; the Letter had a second-order differential equation for centrifugation, and a one-sentence conclusion: the molecule had independent subunits, linked by disulfide bonds. This paper had seven reprint requests in the whole of its life, and people told me the conclusion was impossible. Somewhat later, a man named Franek in Czechoslovakia published a paper in a third-rate journal in which he did exactly what I did. He knew about my work, but he used the Scheraga-Mandelkern expression, which relates viscosity to the sedimentation coefficient. He came up with the same result I did, except that his results had about a 20 percent error. I knew about the expression, but I would never have used it. That paper, on top of what I had done, changed everything overnight. Everybody accepted the result, and, indeed, people started explaining it to me!

By this time, I was deeply immersed in the physical chemistry of macromolecules. When I graduated and stayed at The Rockefeller Institute, I

taught that subject. Having had a chemical background in college, it was very interesting to me. The next step was to analyze the antibody molecule now that I knew it had chains. This conclusion had two implications. One was that you couldn't have done an amino acid sequence analysis of a molecule of 150,000 molecular weight, but if it had chains, there was the possibility of finding the sequence of the smaller chains. The second implication was a remarkable combination of chemistry and medicine. There is a very special disease, called multiple myeloma (the French President Pompidou died of it). It is a cancer of the so-called B cells, cells that make immunoglobulin. At the time the disease was first discovered, it gave rise to the discovery of the second protein after albumin. Liebig discovered albumin, which he noticed precipitated after heating urine. It so happened that a patient in Scotland was dying of this disease which at that time was known as *mollites ossium* — softening of the bones. Two Scottish physicians sent a letter to a man named Henry Bence-Jones who was in the Royal Society of Medicine and a student of Liebig. The letter said (and I paraphrase), we have found a most unusual phenomenon. This man is dying of softening of the bones. When we cook his urine, this protein comes out of solution, but when we heat it some more, it goes back in. What is it? Bence-Jones used his Liebig-style iron retorts and other tools and he came to the remarkable conclusion that this protein was an albumin derivative, the second protein ever discovered. He became very famous, and the substance became known as Bence-Jones protein. It has the following significance in medicine: if you have it, it's almost pathognomonic, meaning that you can be certain that what the patient has is multiple myeloma, the modern name for the disease. There's nothing else that gives that sign. It turns out in fact that there is one more disease, discovered more lately, that does it too. I knew about all of this because it was a medical curiosity.

While I was working on this matter, I found a way of separation, not the best way though. Actually, Rodney Porter, who had denied my work originally, but who came around eventually, devised a better way of doing this separation. I was working with one graduate student on fractionation and it became clear to me that there's something really strange going on. People with multiple myeloma all had either an enormous outpouring of this Bence-Jones molecule of about 20,000 molecular weight in their urine or they had a large amount of immunoglobulin in their blood. Each patient who had the Bence-Jones protein was given over to cells making it and finally died of it; these proteins just invaded everything.

It occurred to me that maybe the Bence-Jones protein is one of the chains of the antibody molecule. So I did two kinds of experiments. First, I tried to get some purified antibodies and compare them to the normal gammaglobulin from the serum of an unimmunized, or just normal, person. A mystery, however, and a really challenging problem, was this: unlike every other protein in your serum, the antibody protein under an electrophoretic separation was just a big smear. No one could ever find out the basis for this smear. People, like Linus Pauling, who had deep theories about antibody production, couldn't figure it out either. This heterogeneity became the focus of my interest, because when I separated and purified antibodies from guinea pigs that were immunized with different foreign molecules, I didn't get a smear, I got a series of bands. Each antibody gave a different band set. I connected that up with multiple myeloma and the Bence-Jones protein, by saying, "Perhaps a myeloma protein could be one pure antibody already created by the cancer which started off as one cell; since one cell makes one antibody, everybody with the disease would have a different one."

I came into the laboratory one day and I said to my graduate student, "I'm going to make Bence-Jones protein out of your light chains." I'd already named the two kinds of chains of about 20,000 and 60,000 molecular weight light chains and heavy chains. He said, of course, "You're crazy." I took his light chains, which he had separated from his immunoglobulin, put them in a tube, and treated the solution in the way you treat urine. It worked! By the way, as a physical chemist, I was also interested in fluorescence spectroscopy. I had been doing fluorescence spectroscopy of denaturation reactions in proteins. The fluorophores in a protein are tyrosine and tryptophan. When proteins undergo denaturation, there's an extraordinary change in intensity and a slight shift in their fluorescence spectra. We did that and we found that every Bence-Jones protein we tested, each from a different patient, had a different spectrum.

The picture emerged first that there was a chain that was not much bigger than ribonuclease, the primary structure of which Stein and Moore had analyzed for the first time. This was beyond what Sanger did for insulin, which had a molecular weight of 6000. They did ribonuclease (molecular weight 15,000), and here we had a molecule with a molecular weight of 20,000. If you sequenced it, you would then know what an antibody looked like in detail, at least part of it. Second, you could get a pure Bence-Jones protein. It was also definitely the case when you took the pure myeloma protein molecule made by the cancer cell in the blood,

which was 150,000 in molecular weight. When you took the light chain from the molecule in the blood and compared it to the one from urine, they were identical. But each patient's protein had a different mobility. When you compared 20 patients, you could be sure you had the answer to the famous question from Dr. Bence-Jones, "What is it?" It is the light chain of an antibody molecule that is made by a single cell, which happened to develop cancer. This cell just grew out independently of antigens and made overwhelming amounts of this pure molecule. It was a wonderful discovery.

At that point it occurred to us that we could do the structure. All we had to do was find a patient with enough myeloma protein. It would be a pure antibody (we didn't know against what) and if we got enough of that, we could start. At that time there was no molecular biology. Sequencing depended on methods of cleavage of the protein chain, and we had to get a pound of this substance. We heard of a patient who had a bad case. He had such a large amount of myeloma protein that it was clogging the arteries of his fingers. They were planning to transfuse him, to put normal blood in and take out his blood so at least for some time he could have blood flow in his arteries. We made a deal that we would help in this effort. We got a jar of myeloma protein, and at this point, we could start to do the structure. This was in 1964.

Things started developing marvelously. You have to remember that biology does not have a strong need for theory, unlike physics. Aside from a bit of chemistry and genetics, theory is really not central to biology. It happened though that the chemical problem of immune recognition prompted a burst in theory making — there was a remarkable explosion of theories. The first was largely identified with Linus Pauling who put forth the so-called instructive theory. That theory said that the reason you can recognize foreign molecules of any rigid structure, even ones that never existed before, is that there is information transfer stereochemically from the antigen to the antibody via van der Waals interactions. It is the folding of the antibody molecules that accounts for their fit. Their single long chain is identical from molecule to molecule, but their folding varies. The complementarity by weak interactions, for which Pauling was so famous, results from the information transfer. While I was working on the problem, it occurred to me that this theory could not be correct. There were three reasons. The first was that it was known that antibodies had two binding sites, and from this the problem of symmetry arose. How could a chain composed of L-amino acids fold around something independently which has a certain

stereochemical structure, say, dinitrophenol, in such a way that it makes two identical binding sites. It struck me that something's wrong there, because it's impossible from symmetry considerations to see how you could fold an L-amino acid chain exactly and identically for each end. It wasn't likely that it had mirror symmetry of sequence — that would be absurd. The second thing that struck me was that there were biological reasons to suspect that you had to take other elements into account. For example, if you had an instructive theory, antigen had to remain around. But there were certain diseases, like yellow fever, which, once you were immunized, you didn't contract again for the rest of your life. You could do a calculation of how many molecules you could possibly have left from the initial infection to the time you died, even if you lived 80 years after the initial infection. The answer was very few. I said, something's wrong here; there must be another mechanism. At that time, Frank Macfarlane Burnet, who won the Nobel Prize in Physiology or Medicine in 1960, came up with a theory that I found more satisfactory, the so-called clonal selection theory. This theory said that you have or make all the different kinds of antibodies you could possibly have and that their production didn't depend on the antigen at all. Each cell made one kind of antibody, and there are of the order of 10^{11} cells. So there is already a repertoire of different shapes that didn't need the antigen to get generated. The theory was in a very Darwinian mode. It said, a foreign antigen went through this library of different antibodies, all in your body, and when it found one with sufficiently high free energy of binding on a cell, it triggered the cell to make much more. So you had three events: a generator of diversity in your body, a polling reaction in which the antigen made enough encounters with different cells in a sufficiently short time, and a differential amplification of those cells with the appropriate threshold for binding. That struck me as a tremendously bright idea and it fit everything we'd observed. I worked very hard to see how this lined up with our experiments.

Actually, I have two stories to tell. One is about a great chemist and the other is about a great biologist. They'll show you how differently successful people can think. I was already convinced that Pauling's theory had to be wrong. By the time I had finished doing my Bence-Jones work and began doing some sequencing, I also had done some work on purified antibodies. It showed a separation picture that wasn't just like a smear. It was heterogeneous but there was some consistency in light chain bands that suggested the conclusion that different antibodies had different chains. I didn't have a model of the molecule yet, but I knew that it had at

least two different kinds of chains and that different molecules had to have different amino acid compositions.

About that time, I was invited to give a lecture at a Kaiser Foundation Symposium. When I arrived in San Francisco, I found out that the first speaker before me was Linus Pauling. His talk was going to be about antibodies and I was going to talk about how his theory wasn't good! I called up a friend who knew Pauling and asked him to arrange for a dinner with Pauling the night before the talk. At dinner, Pauling was with his wife and my friend. All Pauling talked about was nuclear disarmament. It was not long after his Nobel Peace Prize. He was sitting there and talking, and his wife was admiring, and I couldn't get a word in until I finally said, "Sir, I just want to tell you one thing since I have the privilege of talking after you on the same symposium. We've found some very interesting things. The first is that we find that antibody molecules are composed of different peptide chains. Second, the chains seem to have different amino acid compositions for different antibodies." When I finished, he went right back to nuclear disarmament, and I gave up. The next day, he got up and gave a terrific lecture. When he got to the slide of his theory from the *JACS* of 1941, he showed a picture with a tangled chain folding, he said, "This is *one* of the polypeptide chains of the antibody molecule." I said to myself, "My God, he understood everything." When, following my presentation, I got back to my chair, there was a little piece of paper on it: "Edelman, send reprints. Pauling."

The second anecdote is about Macfarlane Burnet, who once came to visit me. My graduate student and I received him, and I said, "I'm so happy that you came because Joe and I are selectionists like you." He said, "What're you working on?" I said, "We're working on the structure of the antibody molecule." He said, "Don't bother with that. Chemistry only makes things more complicated." To which I said, "Excuse me, sir, but if you don't have an analysis of the structure, you can't count how many different molecules there are in the selectional repertoire." "Oh," he said, "mathematics is even worse than chemistry. Look, my boy, don't worry about it. My theory is right. Biology is soft-edged. We don't even call them antibodies; we just call them recognizers." And he walked away. My first thought was, "He's stupid." Of course, I was wrong; he wasn't stupid at all; he was very cunning. But he was also very prejudiced and ignorant about chemistry. He was also right, because his theory turned out to be true. It was a tremendous lesson to me — the two guys, one from chemistry and one from biology. Pauling's mistake was that he didn't

look at two levels at once, he stuck only with chemistry, but didn't look at the cellular phenomena. Aside from our work, the cellular phenomena defeated Pauling because the man who got the Nobel Prize with Macfarlene Burnet, Sir Peter Medawar, had shown for grafting reactions that you could develop immune tolerance. Tolerance is a negative phenomenon; it's like an inverse; you *do not* react to certain things. If you don't react to certain things, how can you have an instructive theory, if nothing is there?

I kept up with my chemistry and even continued with fluorescence spectroscopy. On the other hand, I never felt that I was really central to the immunological community, even though I was a doctor. I was interested in solving the problem. At that point, the choice was whether to finish the whole molecule. This meant certain competition with Porter, who had devised a very elegant way of separating the chains. Previously, Mary Peterman showed that a certain enzyme could cleave the antibody molecule. Porter still thought that it was a single chain. Repeating her experiment, he got a very beautiful result: the active binding part of the molecule came out in one fraction and the other fraction crystallized. That result took over like dynamite, all over the community. It made people even doubt my work. My work said that the element linking the chains is not a peptide bond, it's a disulfide bond. Eventually, Porter came around. We decided to do the structure because we really wanted to find out the origin of diversity. We set out to do this in a rather small lab, and Porter set out to do it in a bigger laboratory with much more expertise in St. Mary's Hospital in London. He was a student of Fred Sanger and he was a very capable chemist; he decided to work on the heavy chain. We decided to do the whole molecule, a huge task. I remember Stein and Moore, particularly Stanford Moore, shaking his head in pity and saying, "You're not going to be able to do it." At that time, I had a very capable group of young men join me. With naïveté and luck, we went ahead and did it. And we did it first. We finished the whole structure. It took about three and a half years of very hard work. Nothing was automated except for the amino acid analyzer, and yet we did the whole amino acid sequence.

Porter thought that the heavy chain contained the antibody-combining site. We felt that the combining site was shared between the two chains. If one chain had p different sequence variations and the other had q, the total number of different sites you could make was $p \times q$. It turned out we were right, and we could finally synthesize the whole picture. The Pauling theory was wrong, the Burnet theory was right in that there was a part of the molecule that contributes to the binding site of each chain which

Rodney Porter (1917–1985) and Frederick Sanger (1918) in Cambridge, 1945 (courtesy of Frederick Sanger).

varies from molecule to molecule. It varies in each particular cell. One cell makes one antibody, so if you have 10^{11} cells, you have 10^{11} different variants.

The next question was, "What is the generator of diversity, G.O.D.?" That is a genetics problem which we did not solve but for which we had a theory. That comes down to what if a code could alter molecules inside the body. Not in the germ cells of the testes or the ovary, which you inherit, but inside your body. That notion was a heresy. The heresy is, "Look, you may lose some DNA, but you don't fluctuate and mutate DNA somatically most of the time. (You can if you're hit by a cosmic ray, but it's irrelevant.)" Here the picture looked like a big combination lock on a safe — you change the combination in one part of the molecule

in your B cells. So we got into the genetics, and proposed a theory ourselves which turned out to be more or less correct, but, of course, not in detail. The theory said that you vary the DNA by recombining it, back and forth, back and forth, and in the end you somatically mutate it. This process makes a different sequence in part of the antigen-binding site, and each antibody you make thus has a different shape stereochemically. All of these results gave the impetus for crystallizing Bence-Jones protein and also crystallizing antibody, and the crystallography was just a beautiful confirmation of the whole story. So the final closure came in when Susumu Tonegawa showed that, in fact, there was somatic mutation and that the mechanism of combining and recombining DNA was true. He got the Nobel Prize in Physiology or Medicine in 1987.

What was remarkable in that period is the amazing intersection of experiments and theories, right or wrong. There was also the unusualness of the antibody problem. We went from medicine to chemistry, back to genetics, and then returned to chemistry and stereochemistry. For me, it was a magnificent experience because I don't believe it's very frequent in biology that you have such a confluence of special things. This is the point. The antibody system is very special. Sharks have antibodies, but lower than that you don't see them. You find them only in backboned animals. This is how I began my Nobel speech: some sciences are important because they are general, others are important because they are predictive, and yet others because they are just downright interesting and bring up something you would never think of. That's what, I think, immunology is about. It reveals a remarkable way of the body solving a recognition problem: how do you recognize stereochemically a great variety of shapes you never saw before. This story also says that you have to watch out for being too categorical in saying that you should have training in this or training in that. The thing you should have is *enough* training and the ability not to reject a field because you've not trained in it, because it may be telling you something very important.

Have you tried to formulate a recipe for scientific discovery?

I'll tell you my theory of discovery by means of an anecdote. Beethoven's landlady says to him, "Beethoven, get out of my house. Your cat drinks my milk, you throw your laundry in the stairwell, and you pound on the piano all night, I can't sleep." He says, "Mrs. Schmidt, don't do this to me. You're my inspiration." And she laughs in response, "Ha-ha-ha-haaa" [the

first strokes of the Fifth Symphony.] That's discovery, namely, contingency, accident, pattern, preconception, elaboration, and constantly playing back and forth against tradition of some kind; in Beethoven's case, it was Viennese classical music. In tracing a discovery there is an extraordinary complexity and diversity in the history, circumstance, cultural development, and technical skill. So to try to lay down any simple rule is not possible.

In any case it was a great joy to me that the Nobel Committee cited my one-page paper to *JACS* announcing the chain structure of antibodies. The episode I told you about was an example of the richness of discovery and of luck, and contrary to what some journalists said, I was genuinely surprised when I won the Nobel Prize. I had never been a member of a scientific coterie and I've never been since. I'm not very good at that. I've never served on a journal, I refuse to serve because I referee papers anyhow, about 30 a year, and I'm not interested in politics. My observation is that, very often, being an editor becomes a powerful position, like being a comissar in certain nations. I hope you don't find that offensive!

You mention in your writings the different levels of organization and you stress that you don't believe in "silly reductionism."

When the story I just told you was over, I didn't lose interest in immunology, but I decided to move on, and look at certain cellular phenomena with the methods of chemistry. This led me to two phenomena. One was cell-cell interaction. This was important for the immune system, but this time I wanted to know about it because of my interest in the shape of the tissues: how do you inherit your grandmother's nose? A deep problem of embryology. It had to depend somehow on cells coming together in a certain order. This much I knew from my medical training. At the same time, I was also interested in the brain because of my interest in biological recognition. It struck me that the immune case was a case of a non-cognitive chemical system and cellular system, which, without any brain, could recognize shapes. I put the brain problem in the back of my head and I got into the field of developmental biology. There are five primary processes that control cells: cell division, cell movement, cell death, cell adhesion, and signaling to induce different differentiation among different tissues. Chemically the most straightforward is cell adhesion. I assumed that there must be molecules mediating adhesion. Again, I ran into a theoretical impasse because people in the field did not believe in that. They believed that cells stuck to each other by electrostatic interactions. My experience said to me, it can't be

right. Knowing the way biology works, there must be specific molecules that are involved in making cells bind to each other. I spent about a year and a half, immunizing animals in a very special kind of assay asking "Could I find an antibody which stopped two cells from binding together? If I could isolate the molecule that antibody was bound to, it would be the molecule that linked the cells together, a cell adhesion molecule or CAM." We isolated the first CAM from the retina, which is part of the brain. When we did the structure, it turned out to have the structure of immunoglobulin! That almost made me faint for this molecule was present in fruitflies and antibodies are not present in fruitflies. It became obvious that the genes that were the precursors of these molecules were also the precursors of the entire system of immunity. Nothing beats experiment. This prompted the second greatest aesthetic response I had since the Bence-Jones experiment I told you about.

I am coming back to your question about the different levels of organization. How do you go from molecules to the cells? Here I'd like to insert something about complexity. Your question about the levels of organization is a very profound one. Even as late as ten years ago people thought that you could visualize biological interactions the same way you did for Krebs cycles or glycolytic cycles or protein structures and everything eventually would fall in place. It turns out that in biology things are more complex.

For example, I worked on cell-adhesion molecules of the brain. The problem was this: everybody believed that the way in which your nerve cells are put together and the order in which they are put together, regardless of complexity, altered how you received signals from the outside world, how you thought, how you breathed, how you smelled and how you would do anything. But how are the cells put together? Roger W. Sperry, who got the Nobel Prize in 1981 for his work on the split brain, and who was a student of Paul Weiss, proposed that the way you put together the brain was by a kind of code almost to the level of the individual cells. This was the so-called chemoaffinity hypothesis.

Somewhat after that, I had been thinking about how the brain works in general. How can your brain recognize so many incredibly different things. Take this room; you couldn't put this room into the computer; there isn't enough sand in the universe to do so. How can the brain do that? It became very clear to me, it cannot be the way you do it in a computer. The brain is not a computer and the world is not a tape with an unambiguous set of signals. Again I must stress that we are dealing

with a chemical system. Identical twins, given the nature of the immune system, do not recognize the same antigen molecules by the same antibodies, despite the fact that their reactions to those antigens are more similar than the reactions of non-identical twins. I was obsessed with this problem. It seemed to me that this was the central problem: how can we recognize, how can we perceptually categorize the world in a way adaptive to our species?

Here is an example of the curious influence on practice of thinking about theory. I said to myself: "If Sperry is right, your theory that the brain is not a computer is doomed, there'll be a code. So go see how cell-adhesion molecules work. If you're right, you won't prove your theory but at least you won't disprove your theory. If the theory is right, cell-adhesion molecules should change according to locale and they should not be determined by a code. While they should come in a few specificities, they should be influenced by the past history of that cell and, if so, then even identical twins should not have an identical hook-up system in their brains." My colleagues and I proved that. We showed that that's how cell adhesion-molecules work, dynamically and combinatorially.

At this point I'd like to tell you something about degeneracy which, to my mind is as important to biology as symmetry is to physics and chemistry. Consider the problem of redundancy: you send up a rocket, but you're scared because there are no engineering shops up there, so you send five computers that are identical. You use one at a time; if one goes sour you call up no. 2, or no. 4, it doesn't matter, you're redundant. But the structures are isomorphic. You don't send up different kinds of computers with different kinds of programs. You send up one kind and you repeat it. Degeneracy is different. By degeneracy I mean a system in which systems of non-isomorphic structures lead to isofunctional results. It doesn't matter if the two structures are at two different levels of organization or if they're companion molecules with a big structural difference, or if they're networks. The most startling thing in biological systems is that different structures at different levels can do the same thing. They weren't *designed* to do the same thing because evolution doesn't design anything. Given the nature of the complexity in a biological system it's inevitable that degeneracy comes in. Thirty percent of the mutations of flies are lethal, but the rest are not: almost seventy percent are non-lethal. If there were no degeneracy, all mutations would be lethal. Degeneracy is a very deep and important principle in biology and particularly for the brain, and we don't yet understand it fully.

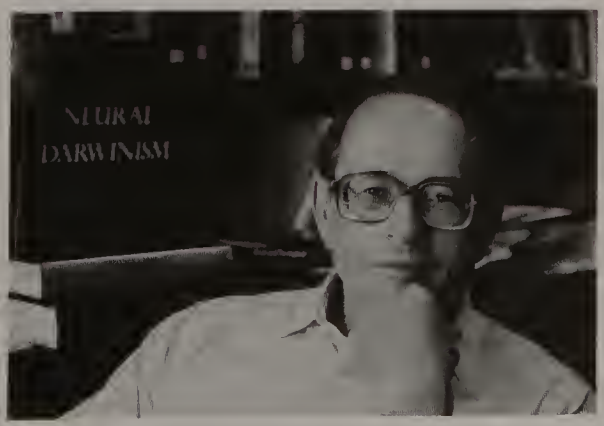
Any attempt to resolve the networks of complex biological reactions, even if you define individuals in terms of some unitary causal chain, in general will fail. Biological systems by their nature are degenerate systems, because evolution can't go back to the drawing board. Every time something is maladapted, you have to call upon something at some level that'll add something to the structure. Very rarely, maybe with viruses, you can go on simplifying, but you can't, in general, go back and redesign the whole show. So the system continually increases in complexity. Most mutations are deleterious. By nature, they're random or close to random, so how can you keep them from knocking you out? The answer is, at every single level of organization, biological systems have degeneracy as a result of their complexity. This is very interesting because it says that we have to get measures of complexity from biological networks just in the same fashion as we got measures of thermodynamics from the Carnot cycle. We may not have a complete theory of complexity very soon, but we need measures of complexity and measures relating complexity to degeneracy. This is what I'm currently working on.

Finally, we can talk about reductionism. Every science, methodologically, must be reductionist. However, in thinking about degenerate systems, every person, for example, is unique, and cannot be described as a bag of molecules and their interactions. I am told that when Einstein was asked this question, "Do you think science is exhaustive?" the old fox smiled and said, "Probably, but what is the use. It is like describing a Beethoven symphony in terms of air pressure waves." I've had a small quarrel with the physicist Steve Weinberg who said that ultimately you must reduce everything in terms of some ultimate supersymmetry equation when we get the four forces together. That strikes me as really foolish. My counterargument is that the laws of physics may even not have changed since the Big Bang, but the initial conditions are far from equilibrium. Since we all agree that it's very likely that there was a Big Bang, and we are far from equilibrium, the history is not fully determined because of the changing boundary conditions. Weinberg criticized me after he read my essay on *Silly Reductionism*. He said that Edelman doesn't realize that we will have to relate everything to the theory for the four forces, except for historical accidents. To which I say, "Weinberg, you are a historical accident, so am I, and so is evolution." This is the issue. Biology revolves around historical accidents, but the miracle is that they are composed of complex systems of chemistry. These chemical systems and biological systems have been composed via complexity and degeneracy in such a fashion that they're able to map onto unforeseen

circumstances. Therefore the notion that you can get a non-statistical reduction is foolish. That is to say, biology will be indeterminate to the extent that in order to get a complete understanding of these high-order chemical systems, you need statistical methods. You'll never be able to do it any other way. It isn't going to come down to a perfectly clean circuit like an electronic circuit. There's nothing mystical here, but it's very intriguing.

You have introduced the expression "Neural Darwinism" and Manfred Eigen uses this expression "Molecular Darwinism." Is there a connection?

Not really. I think we both believe that we should not confuse the mechanism of selection for the principles of selection. Certain people, like Francis Crick, don't seem to understand that. Crick attacked me and used the expression "Neural Edelmanism." In terms of principle, selectional systems all have three constraints: (1) You must have a generator of diversity (G.O.D.). (2) You must have some mechanism for polling so that two domains which have no causal connection can sample each other with sufficient completeness. In the immune system, if I didn't poll, the antigen and antibody molecules would be kept separate, and I would die. (3) You have to have some form of differential amplification, providing a selective advantage, for example, by producing enough antibodies of the right kind. These three principles have completely different mechanisms in evolution, immunology, and brain science. Speaking about molecular Darwinism, as Eigen does, refers simply to a particular mechanism under principles which are themselves Darwinian. But natural selection is only one of many mechanisms. It is perhaps the biggest, but there are many others by which evolution takes place. We



Neural Darwinism and Gerald Edelman (courtesy of Gerald Edelman).

have to separate principle from mechanism. And, of course, any use of an adjective next to Darwinism is dangerous if it isn't spelled out. One of the worst uses was social Darwinism.

Neural Darwinism is a theory, not a simple definition. It has three basic mechanisms: the first is that when you wire up the brain, while there's a genetic constraint on the wiring, no two individuals wire up the same way. You create diversity in the wiring. You do it by selection of different neural circuits. This is called *developmental selection.* The second principle of neural Darwinism says, when you get to a certain stage, an overlapping process doesn't change just the structure but also changes the synaptic efficacy, favoring a kind of traffic control. This is called *experiential selection.* No two individuals do it the same way. The third is a truly original and very difficult idea for many people to understand. There are mappings between brain maps, which involve massively parallel recursive circuits. They are not like feedback at all. Feedback has only one wire on each way; if it had four wires, it would have 20 different ways of deciding what the neural signal was and it wouldn't know what correction to apply. Brain systems are not instructional like feedback circuits; these systems map maps and correlate chemistry by spatial-temporal coordination amongst maps to make new maps. Those three mechanisms together are neural Darwinism. By the way, the repertoire of the brain makes the repertoire of the antibodies look silly. Graph theory helps in appreciating it. If I take nine vertices and ask, how many graphs can be made with the same types of edges going to the same types of vertices, I'm already up to 330,000. George Pólya had a theorem about this. Looked at this way, the brain is a graph with a hundred billion vertices, a hyperastronomical number.

At this point I'd like to add something about a theory that has not been completely worked out yet. We have found that the selectional system of the brain cannot work except if you're already born with a value system. What is the place of facts in the world of value? The view of science from a very reductionist point of view can give me a theory of everything except of a physicist. He is excluded because a physicist has a God's eye view; he already assumes sensation and perception, which are not included in his theories, as Schrödinger pointed out. If you think about the degeneracy and complexity of the brain, you begin to see that what counts is what makes a difference to the system; not some external observer looking down like God. The reductionism of God is one thing, but it leaves out history and people. We find that you cannot make a selectional theory of the brain-work unless you have actually put in a value system. We've done

a huge computer simulation, one of the biggest in the world on neural systems. We find that it consistently fails if we don't put in something like this: light is better than no light or darkness is better than light. We don't put them in as words, we put them in as the consequence of chemical reactions. We've worked on the theory of value and have found that, in neural systems, we can have value from evolution. But what does it mean to be a human being? Possessing modifiable value, so that learning can alter your value system. There are certain ascending chemical systems in your brain related to your value system and if learning can modify this value system, you can do certain things other animals can't do.

We are at a funny stage of our progress. It's not going to be so simple to go up from molecular structure even of macromolecules up to cells, up to cell interactions, and up to brains by using the same kind of arguments. There are three sets of complex systems that we have to wrestle with today. The first is the chemistry of the cell itself: how macromolecules in the cells make structures of supramolecular assemblies and how they transfer signals. The second is in gene networks. In my opinion, genes are not blueprints of the body, they're constraints on the chemistry of the body. There is a big difference in these two views. Genes form networks, as the old geneticists recognized, but not many new molecular biologists do. They think that when we get the whole genome, it's all going to be over. The fact is, gene networks are degenerate. The biggest of all networks is that of the brain. Here's a paradox. I believe, we'll solve the brain before we solve the cellular chemistry. The reason is neuroanatomy. That anatomy is a deep constraint on the brain and we have so many methods to look at its networks that we'll learn about their governing principles before we learn about those of the cell.

I'll give you two examples of the difficulties posed by cellular chemistry. There are about two thousand kinases and about a thousand phosphatases in one of your cells. These form unbelievably complex networks. Just because I found a path showing this molecule links to this, and that links to the nucleus, I may have a necessary but not a sufficient description. Now consider the problem of transcriptional regulation. The promoter part of the gene accounts for how transcription starts, to transcribe the actual gene into RNA, which is finally going to be spliced, and go out to the cytoplasm and serve as template in making protein. When you look at the DNA stretches that form the basis for binding of proteins so that these transcriptional events occur, what you see is nucleotide stretches about 12 to 20 bases long, but you also see such a combinatorial richness that it makes you

tremble. If you look up two species, which are making the same homologous protein with the same developmental function, some of the same DNA motifs may be 10 kilobases away from each other in the two species. One is trying to understand all the different ways in which these combinations can occur even for one protein in different tissues and different contexts. This problem is of staggering proportions. We are working on it, and so are others, and I believe that, hard as it is, it will be solved before the problem is solved of trying to see how various protein–protein interactions are occurring in the actual cell in time periods of 300 milliseconds.

My personal belief is that all these complex biological networks will follow very similar routes because their guiding principles are similar even though the mechanisms are different. Right now the central problem of biology is to understand such networks. We're now passing to a period in which the reductionism of DNA and molecular biology is going to have to be interpreted in terms of this kind of analytical understanding of biological networks. What will emerge, I think, is going to be a theory like statistical mechanics.

To try to really understand complex multilayered systems with constraint theories will be a tremendous challenge for both chemists and biologists, and eventually for physicists and mathematicians as well. It will have to do with appreciating systems that can develop, systems, which can be adaptive without having a plan or an algorithm. Take feedback control as an example. There's a very sophisticated control theory in engineering, even for non-linear cases. The problem with biological systems is that they weren't designed: you just select the individual to survive. Anything that happens to be in that individual is OK for the time being. On the other hand, you can cut out large chunks of complex networks in that individual and the system keeps functioning. It can adapt although it was not *designed* to adapt. When we learn to simulate such networks, a whole new horizon will open up for both science and engineering. It will also be a renaissance for chemistry.

In your latest book about the last frontier, understanding consciousness, you stress the importance of symmetry and memory.

Symmetry has a tremendous degree of generality. It is a central principle in science, particularly in relation to the conservation laws and the fundamental equations of physics. The other important notion is memory. I don't mean something like computer memory. I mean our own memory, which I'd call non-representational memory. When DNA arose in the RNA world,

covalent bonds could reflect historical selection events. So while the determinism of local chemistry was an important constraint, it was not the answer to what the DNA sequence was during inheritance because that depended on selection from a higher level. This sequence constituted a form of memory, but since a number of other DNAs could also have played the same role, there is degeneracy. This is a curious kind of memory; it is not an exact thing and it's not even a precise deterministic chemical structure. Then there's a new event, and there is autocorrelation between past events and the new event that had never occurred before. In most chemical reactions and even in the evolution of stars, there is no such inheritance, no selection of a certain set of traits to match an environment that you can't predict. When you come finally to the brain, defining the nature of memory is a truly staggering challenge. I can only give you a feeling about it. Most people in neurobiology think that your memory is representational. They think there's a code in there. I don't believe that at all. I think your memory is more like this: imagine a glacier and imagine changing weather. The weather is the signal, the glacier is the substance of the brain, and let the rocks down the mountain be the neural connections, and a pond at the bottom the output. Now the weather changes, the water melts, it goes down, crisscrosses across the rocks, and it finally reaches the pond. Then the weather freezes and then it warms up again and there's a different pattern as the melted water gets down to the pond. Every once in a while a path can be so deviant that it connects to another pond, or the two ponds connect eventually, but maybe they don't. By these means you made an association. That's how your memory works. You don't have a replica, you recreate, under the constraint of a network, a possible output from non-isomorphic possibilities like the different pathways of water trickling down. But these non-isomorphic possibilities still have something in common under constraint. Now generalize this example to n-dimensional space. That's what your memory is. It consists of you recreating a kind of output under constraint. That's one mechanism behind memory — the *principle* itself arose in nature when life arose.

Speaking about consciousness, I wrote a book about it in 1989, some time before the consciousness craze began. For all the intervening time, however, my colleagues and I lacked an experiment. Now we have completed an experiment and have just sent in our paper. You're the first person I'm talking to about it outside my laboratory.

We all know what consciousness is. It is what you lose in deep sleep and recover when you awaken. We all know that when you're hit on the

head, you can lose it, that's it. If someone gives you general anesthesia, good bye. I had major surgery about three and a half years ago. I'm a doctor and I have a little imagination, which is not good. The anesthesiologist came in and said, "You know I read your book and I really don't understand this re-entry; what do you mean by spatial-temporal correlation?" So I started talking to the guy and he thanked me and said, "So that's what it is." And 9 minutes later he said, "This has been fascinating, Dr. Edelman, but I'm afraid we have to say good-bye to each other for a while." Then it was just bang, gone, not anything, the film just stopped. So you know the brain is involved in that. But what's the difference between a conscious input and an unconscious input? That is the question my colleagues and I asked, and here's what we did. We set up a magnetoencephalograph, which uses quantum mechanical sensors to measure magnetic fields associated with brain currents. These are not volume conductor currents and are not like EEG. Even if you can't recompose all the vectors you can measure the currents about two inches inside the head through the cortex. We applied a very interesting, known classical example called binocular rivalry. Put on a red lens and a blue lens, and simultaneously present vertical red bars and horizontal blue bars. Let the guy look at them both through these glasses. But the red can go into only one eye and the blue can only go into the other eye. It is a well-known fact that you either see one pattern or the other and you switch from one to the other. This switch is out of your attentional control. This is a kind of involuntary consciousness. People have different switch times and it's not regular. There is one guy in our lab who is marvelously close to regular. Every 2–2½ seconds, he switches from one pattern to the other. If you see it, it's quite startling. You can see only one of the two at a time but you know the other is going in too. People have measured it with electrodes in animals, but we did it in humans because, given their ability to report, you know you're secure about consciousness.

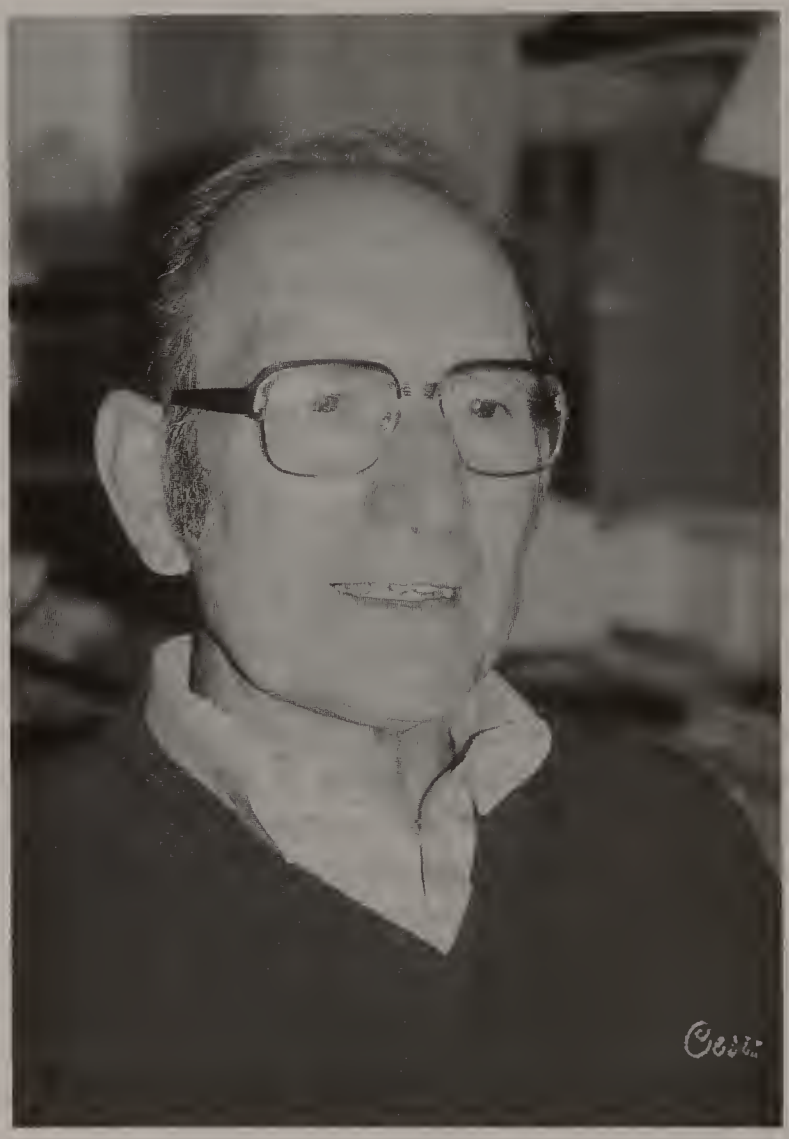
Here's our discovery. By a detailed Fourier analysis we've been able to show that you can trace which brain waves come from which signal. We can tag each signal by flickering each at a different frequency. Then we say to the guy, "Whenever you see the red, flip the right hand switch and whenever you see the blue, flip the left-hand switch." He's sitting there, and flips, flips, flips. He doesn't know what we're doing and we don't know when he's going to flip. When we analyzed the data we found, contrary to the animal reports, that even when the guy is unconscious of the blue pattern, a large part of his brain is occupied and showing

signals. We can plot that out and calculate it. Now, when he sees the red pattern you get as large a part, but local areas of the brain also light up like crazy so that you can see the difference between the conscious and unconscious state. The difference can be seen by subtracting one set of evoked potentials from the other. Statement: even when you're unconscious, you're using a large part of your brain. When you're conscious, for the most part most of the difference spectrum goes plus in special local places, but some also goes minus. And every individual does it in his own way. I can actually look and say, "This person was conscious of the red, and I can even identify him as an individual." This doesn't sound like much, but it's a really tantalizing experiment. It opens the possibility of relating the properties of consciousness for the first time to the understanding of memory and perception. While I'm really excited about this I realize that we must be very clear about the limits of science. Being is not describing. If I describe a complete scientific theory of consciousness, by which I mean, if I say when I do this you will do that, the experiment will never give me the notion of *feelings* of this or that. For this I have to have a body, and not just any body, but a body with a specific history and one that recognizes language. If I could make a thing, which had that structure, it might report green, warm, and so on. Unfortunately, there is a peculiar expectation in some sectors of the consciousness field that says that you ought to be able to give a Martian a description of what green and warm is and he will grasp that experience. John Locke in his wonderful essay speaks of this blind man who finally understands what crimson is; he says "It's the blaring of a trumpet." It is enough that science describes experience. One doesn't expect it to recreate experience.

There is then another interesting thing about the expectations of science versus the expectations of human experience. We will fully understand the basis of consciousness some day but all that will do is tell us what formally correlates with what in the course of things. If you ask why is there something rather than nothing, I might tell you the anecdote about the two old Jews drinking tea Russian style. One says, "You know, Max, life is like a glass of tea." The other says, "Why, Louis?" And Louis answers, "How the hell do I know, am I a philosopher?"

References

1. Edelman, G. *J. Am. Chem. Soc.* **1959**, *81*, 3155–3156.



César Milstein, 1998 (photograph by I. Hargittai).

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César Milstein

César Milstein (b. 1927 in Bahía Blanca, Argentina) is a retired (active) Member of the Staff of the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB), Cambridge, U.K. Dr. Milstein shared the Nobel Prize in Physiology or Medicine in 1984 "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies." The co-recipients were Niels K. Jerne (1911–1994) and Georges J. F. Köhler (1946–1995), both of the Basel Institute of Immunology, Switzerland.

César Milstein started his higher education at the Colegio Nacional in Bahía Blanca in 1939 and completed it at the Universidad de Buenos Aires with the degree Doctor en Química in 1957. He worked at the Instituto Nacional de Microbiología in Buenos Aires between 1957 and 1963, with the period 1958–1961 being spent at the University of Cambridge in the U.K., where he received his Ph.D. in 1960. Since 1963, he has been at the MRC LMB, where he has held the post of Head of the Protein and Nucleic Acid Chemistry Division and also the post of Deputy Director of LMB.

Dr. Milstein has received many awards and recognitions. He has been Fellow of the Royal Society (London, 1975), Foreign Associate of the National Academy of Sciences (U.S.A., 1981), and a Member or Honorary Member of many other learned societies. He received the Wolf Prize (Israel, 1980), the Robert Koch Prize and Medal (Germany, 1980), and the Lasker Basic Medical Research Award (U.S.A., 1984), among many others. The Royal Society has awarded him the Welcome (1980), Royal (1982), and Copley (1989) medals.

Our conversation was recorded in Dr. Milstein's office in the Laboratory of Molecular Biology on October 8, 1998,* and was later augmented as seen below.

First, I would like to ask you to summarize your Nobel Prize-winning research.

The prize-winning work was performed over 20 years ago. Today we have a different perspective, and what was an achievement then is more or less taken for granted now. The concept of cloning, for instance, had a different meaning 20 years ago. Our work contributed to the changing perspectives about cloning.

César Milstein as a Ph.D. student in 1959 at the Department of Biochemistry, University of Cambridge (courtesy of César Milstein).

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At that time there were many mysteries in the world of immunology. We did not understand at all the origin of antibody diversity, the antibodies being those molecules capable of recognizing any antigen. There were millions and millions of potential antibody molecules capable of recognizing millions and millions of antigens. Any chemical injected into a human would eventually generate antibodies, although the body had never seen these molecules. Once your body invented such an antibody, it would remember it, and the body knew much better how to respond to an invader if it had attacked the body previously. This is the principle of vaccination.

In the early 1970s, the mechanism of antibody diversity was not yet understood. I was working on this problem and I supported the idea that the creation of antibodies was the result of somatic events, which involved changes in the genetic makeup of the immunoglobulin genes. You inherited a small number of genes or fragments of genes and then there were somatic events. At one point I favored the somatic point mutations, which were generated at a very high rate in specific regions of the gene. We had a hypothesis about that. Those changes were creating constant diversity. The question was how to demonstrate such diversity.

In 1970, we started experiments using myeloma cells in culture. These are B-cell tumors which secret myeloma proteins. These proteins are structurally the same as antibodies but, since they are made by tumors, they are directed against unknown antigens. The idea was to see if such cells mutated their myeloma proteins as we predicted for antibodies. This was a mammoth experiment involving analysis of 7000 individual clones. We did indeed find mutants, but they were not of the type, which could explain the expected diversity of antibodies. In parallel, we also started using myeloma cells in culture to understand why only one of the two chromosomes produced antibody. This is known as allelic exclusion; only one of the two alleles makes the antibody. The question we set out to investigate was whether fusion of two myeloma cells will produce hybrid cells co-expressing both antibodies or not. The experiments were largely the work of an Australian postdoc, Dick Cotton, and the result proved that the allelic exclusion was not operative in hybrids. In other words, hybrid cells were capable of expressing both myeloma proteins and indeed random combinations of light and heavy chains of both parental cells.

All this work attracted Georges Köhler to come as a postdoc from the Basel Institute of Immunology to join my group. His project was to grow a myeloma cell in culture capable of recognizing an antigen, in order to derive mutants with altered affinity for the antigen. Fortunately, he failed! He also

César Milstein and Georges Köhler during an international meeting in Kenya in 1979 (photograph by Celia Milstein).

started a side project, involving variations on the theme of hybridization of two myeloma cells. The combination of the need of antibody-producing cells in tissue culture, which could not grow, and the experiments with hybrid myelomas did the trick. Why not try to make the cell we needed? Perhaps we could substitute one myeloma cell for an antibody-producing normal B cell? Normal antibody-producing B cells die very quickly, but perhaps we could immortalize the antibody production by fusion with the myeloma cell line? To our surprise, the experiments were a resounding success from start to finish. Within a short time, we derived cell lines in culture making antibodies against preselected antigen. The antigen of choice was sheep red blood cells because the secreted antibody was easy to analyze using the plaque assay technique developed by Niels Jerne. So we could now look for mutants. This search turned out to be terribly disappointing. So, at the time, the initial purpose of the technique was lost. The twist of the story is that much later the technology turned out to be an essential step forward in analyzing the problem of origin and nature of antibody diversification.

On the other hand, even before our *Nature* paper was completed [Köhler, G.; Milstein, C. "Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity," *Nature* **1975**, *256*, 495–497], we realized that the

continuous production of antibodies by immortal cells in culture had interesting potential for industry. Until then, antibodies, which were used extensively, for instance, in passive therapy and in diagnosis, in radioimmunoassays, and elsewhere, were produced by injecting animals. This was a crude way of producing antibodies. Production plants depended in some cases on a couple of rabbits, which had been immunized to produce the desired antibody. We pointed out the potential usefulness of our procedure in our *Nature* paper. So we decided to explore the possibilities of the production of useful antibodies. By then, Köhler had returned home but I started other collaborations internally and externally.

It occurred to us that since we were immortalizing a single cell out of a large number of cells, this offered an interesting possibility. The antibodies that come from a serum constitute an enormous mixture of millions of molecules. Even against a single antigen there are many of them and they are very different. But each cell makes one antibody. It secretes it into the serum and in the serum they all get mixed up. They are polyclonal antibodies.

Let me give you an example at this point. In blood transfusions, the blood from one individual is transfused to another individual. If the two have different blood groups, the recipient will make antibodies to the blood group which he does not have. Of course, the red cell contains many other antigens in addition to the blood group. Because the other antigens are common to all humans, the individual will make the anti-blood-group antibodies and will ignore all the other antigens. The serum of the recipient is the traditional reagent to define blood groups. However, if you inject the same red blood cell into a mouse, the mouse will not only recognize the blood group but will also recognize all the other antigens that differ between the human and the mouse. Thus, the serum of the mouse is useless as a reagent because it recognizes all the blood cells being human rather than being of a specific blood group. If you now fuse the spleen cells of the immunized mouse, you get an immortal population of cells containing many hybrids, secreting as many different antibodies as those present in the serum. Because they are immortal cells in culture, you can clone them, you can make clones of individual cells. Since each cell makes one antibody, each clone of that cell will be a monoclonal antibody. That is the idea of the monoclonal antibody.

Most of the monoclonal antibodies secreted by individual clones will recognize antigens common to all humans. But some will recognize the blood group. There we have a way of making an anti-blood-group antibody

in a mouse. This was totally impossible in the past. And not only that. You can make many of them, you can select the best ones, and that will become a chemical reagent, which is made by a little factory called a cell hybridoma. You can store it, you can sell, you can distribute, and you can make hundreds of liters of it. You can thus make reagents for blood grouping. In fact, today the blood-group reagents are made in that way.

Did you patent this?

The patent story is a complicated one. Our laboratory developed commercially exploitable antibodies as blood-group reagents. We also developed some other commercially useful antibodies, as well as a new cell line to derive rat hybridomas, which were patented.

However, the original procedure of making monoclonal antibodies was not patented. In those days, the inventions made at MRC could be patented only by the National Research and Development Corporation (NRDC). MRC sent a preprint of our paper to NRDC, but they did not find any patentable feature in it because there was no product. They argued that you could not patent procedures using live organisms. This is the real dilemma although there were many different stories told afterwards. The NRDC at that time did not have the courage and the push to try to impose new criteria on patents of this type. Thus, the procedure of producing monoclonal antibodies was not patented. Later on, individual elements of this story were patented, in some cases even against the advice of NRDC. Since then, the whole legislation changed and this problem does not exist anymore.

The interferon patent itself is an interesting story. It illustrated the use of the technology. Interferon is an important agent against tumors and it was being tested for treatment of colds but it was not pure. It was made in tiny quantities by cells in culture, and nobody could purify it. It could be detected though in impure preparations by a biological assay. Based on that biological assay, David Secher decided to try to go the other way around. Instead of purifying interferon, and then making an antibody, he decided to make an antibody and use the antibody to purify interferon. Even if interferon was in a very tiny amount, if you injected it into an animal and the animal made the antibody to that interferon, there would be some cells making that antibody in addition to many other cells making antibodies to all the impurities. So the problem was to identify the hybridoma clone producing anti-interferon amongst the hundreds of irrelevant clones. This was possible because the anti-interferon monoclonal antibody secreted

César Milstein with David S. Secher at the Laboratory of Molecular Biology in 1980, when anti-interferon was made (courtesy of César Milstein).

by the wanted clone was able to deplete the biological activity of the impure preparations of interferon. In that way the correct hybridoma clone could be identified and propagated so that large amounts of the monoclonal antibody produced by it could be put in a column on an insoluble support. Then, passing a very impure culture of interferon, we would retain the interferon and nothing of the rest, and elute pure interferon attached to the column. That worked like a bomb. It was a fabulous procedure and it was patented. The patent has stood the test of time although it had been contested. This procedure and the antibodies to red cells were the most successful and served as basis for creating Celltech, which is now an important biotechnology company in Britain. I was involved in it only in the early days.

What turned out to be the most important breakthrough of the hybridoma technology was this idea that you could use it to identify new components of the cell surface, particularly those described as cell differentiation antigens — that is, components of the cell surface which differ from one cell to another. These components are often connected with the specific functions of the differentiated cell. The white blood cells were particularly interesting for us. For instance, lymphocytes are a very complex population but they are indistinguishable from each other. For instance, B and T lymphocytes look

the same. However, even then, they were known to differ in the components of the cell surface and indeed could be distinguished using antibodies. However, such antibodies were difficult to prepare and they were precious reagents of very limited value, recognizing only a few differentiation antigens. We strongly suspected that this was a tiny tip of the iceberg. Perhaps lymphocytes included even more complex subpopulations that could be unscrambled using hybridomas.

The idea then was that instead of purifying unknown antigens, you make monoclonal antibodies to each one. Then, with the antibody you can purify each individual molecule regardless of the mess in which it is. This was the real birth of the hybridoma revolution. The man who was the key collaborator in this was Alan Williams, who tragically died at the peak of his career. We published the first paper in which new differentiation antigens were defined in 1977 [Williams, A. F.; Galfrè, G.; Milstein, C., "Analysis of Cell Surfaces by Xenogenic Myeloma-Hybrid Antibodies: Differentiation Antigens of Rat Lymphocytes." *Cell* **1977**, *12*, 663–673], two years after the *Nature* paper. We discovered the rat CD4 antigen, the homologue of the human, which is used by HIV, the virus of AIDS, to infect our T cells. A huge development followed and a series of international symposia was initiated. There are now many molecules identified in similar ways as components of the cell surface. They are important not only for basic research but also because they are the basis for making new reagents for chemotherapy.

The most important impact, however, was in diagnosis. Just consider the pregnancy test, which women can do themselves in the privacy of the toilet with a little stick and a little sample of the urine. It had the biggest early impact in the application of the monoclonal antibody technology.

In therapy it took a much longer time to apply monoclonal antibodies, but now there are successful products on the market. At some point, people were hoping that tumor-specific monoclonal antibodies could be created, but it turned out to be not as simple as that. It took a long time to develop monoclonal antibodies that can be used in therapy, but there are now three or four such reagents in use against specific tumors.

By 1980, when the industry became aggressively interested in developing further products, I thought that my job had been done. I became interested in developing methods to manipulate antibody genes and, later on, to bypass the animals and make antibodies in different ways.

At this point I have to go back in my narrative to the diversity of antibodies. In the mid-1970s, there were important developments in

genetic engineering, and the complexity of the genetic makeup of antibodies was understood. There are two chains in antibodies, a light chain and a heavy chain. Both of them are made of gene fragments, two for the light chains and three for the heavy. However, each of the fragments is encoded by families of fragments so that during B-cell development, individual fragments from different families are fused together in a combinatorial fashion. This was demonstrated by Susumu Tonegawa and earned him a Nobel Prize in 1987.

The joining of the fragments is imprecise, and a lot of rubbish can get in between, random pieces of DNA, for instance. This introduces changes in the structure and contributes to the diversity. This is a major source of diversity created during the life of individuals. Individuals are born with a simple genetic makeup but by putting these fragments together, enormous numbers of variants occur, in the order of 10^7 or 10^8 different molecules. The diversity, however, is concentrated in the area between the fragments. That region is one of the binding areas of the antibody, not the only one though. There was a strong belief that other binding areas could also change by mutation.

I told you at the beginning of this interview how we failed to detect those types of somatic mutation in myelomas. In 1980, I returned to this question. I reasoned that we could use hybridomas to dissect the immune response to a given antigen. From the early days of immunology, at the turn of the century, it was first suspected, then established, that there was a maturation of the immune response. When you immunize an animal and you immunize it again and again, the antibodies being produced in response are not only easier to elicit because the individual has a memory to make them faster, but they also improve in quality. We set out to look at the immune response of an animal and to follow it with time. So we took a small antigen, a hapten, the old haptens of Landsteiner, to get a very simple immune response. Then we immortalized the cells that make the antibodies to that hapten and examined how do they look and how do they change with time.

This was how we discovered that the process of the maturation of the immune response, the improvement of antibody quality, was largely by somatic mutation. So, you see, in an animal there is a large variety of cells which encounter the newly infected antigen. There are so many different cells expressing different antibodies that some will interact with the injected antigen in one way or another. Now you begin to somatically mutate the antibody genes of those cells. The maturation of response involves changes

in amino acids along the chain. The potential for diversity is enormous. Most variants are likely to be deleterious, but others may improve the affinity for antigen. There is a mechanism in the organism, which is still poorly understood, in which the antigen selects those cells that are making a better mutant. We seem to have a micro-Darwinian system built into our immune system whereby mutants are produced and are inherited because the clones grow up and the daughters of one cell reproduce the same mutant. If those mutants have improved capacity for binding the antigen, they will survive while the others will not. If you like the expression of the survival of the fittest in the old Darwinian sense, here we are talking about better fitting the antigen in order to survive.

The inherited properties you mentioned here are from cell to cell, not from individual to individual.

From cell to cell. Once the individual is dead, the whole system is finished. Each individual has his or her immunological history. What we inherit from individual to individual is the potential to do it.

We inherit also other things. Evolution actually helps in shaping the raw material. For instance, one thing we have discovered recently is that this somatic mutation is not completely random. It hits preferentially at certain segments. We are actively working on these problems at this time.

Darwinian evolution evolved these molecules to make more variable the parts of the antibody that you want to vary most. Although there is a micro-Darwinian evolution going on for the creation of the antibody specificity you want, there is also a real Darwinian evolution to shape the genes to make them more focused to the flexibility appropriate to their function.

We have learned all this from producing monoclonal antibodies, at different stages of their responses. Developments in technology have also helped this work. Sequencing techniques and PCR (polymerase chain reaction) were important in learning about interactions between the genes and between the antibodies and antigens. We can now crystallize monoclonal antibodies and study them by diffraction techniques, and we can look at the way in which the antigen fits into the structure of the antibody molecule; we could not crystallize them before the production of monoclonal antibodies. We are also learning how these processes take place and about the strategy of the animal to produce antibodies. Then, in the last 10 years, bacteriophages were introduced to derive antibody-like molecules. Using pieces of DNA copied from human white blood cells and recombinant techniques, my

César Milstein with Michael Neuberger, FRS, and Greg Winter, FRS, his two colleagues involved in antibody engineering, in 1998 (courtesy of César Milstein).

colleague Greg Winter has been able to produce huge libraries of antibody combining sites. As in naïve animals, these naïve libraries contain phage particles capable of recognizing any antigen. The specific monoclonal particles can be isolated and grown. The hope of producing antibodies without the use of animals is now a reality and is particularly useful to produce human antibodies.

The next stage is to try to imitate the maturation of the response, which is more difficult. Thus, things are moving ahead although the traditional way of making hybridomas is still very useful. Furthermore, the method has received a new lease on life by the work of my colleague Michael Neuberger. He derived transgenic mice, in which the antibody genes of the mouse are replaced by human genes. So when the mouse responds to antigens by producing antibodies, it uses human genes and, accordingly, the mouse produces human antibodies, which can be immortalized using the old-fashioned monoclonal antibody technology.

Would you care to comment on the possibility of cloning humans?

I think it is horrible. It would be a terrible stupidity.

How about changing the germ line in individuals?

I am also very much against it and agree with the official science policy in Britain that you should not do anything with the germ line.

What if it can cure an inherited disease?

I am still against it. I would like to see these things first in animals. At the moment, the whole technology is very dicey. We do not know how much such changes could affect other areas. Until I have much better evidence of feasibility in animals, I will be dead set against doing anything in humans. Once this is shown to work in animals, I will think again.

Is this resistance technical or ethical?

In the case of curing disease, it is technical more than ethical, although there should also be ethical considerations. It is a very complex issue and goes well beyond the science itself. But first the science must be absolutely safe. Once it is safe to do, then it is up to all of us, not only up to scientists, to decide whether to proceed or not to proceed.

Could we now go back to your origins?

My father went to Argentina when he was 14 from a little village in the Ukraine, about 200 kilometers south of Kiev. My mother was born in Argentina, but her family had arrived in Argentina from Lithuania some years before she was born. Both families were Jewish. At that time, it was a frequent destination for Jewish families to emigrate to Argentina. Baron Hirsh made an arrangement with the government of Argentina to bring Jewish immigrants, who were subjects of persecution in Russia, to Argentina. This wave of immigration was at the end of the last century. The immigrants all started as land workers, and so did my father. My mother, being in the first generation, went to school and to college and became a teacher. She was very successful and was a headmistress. My father eventually became a reasonably successful businessman. We were three brothers, and all of us went to university. For my father the most important thing was to send his children to university. This is a very Jewish attitude. No sacrifice was too high to give your children education. My two brothers became engineers. One of them is still alive. My mother lived long enough to see me settling down in Britain and doing well in science; she died though before I became Fellow of the Royal Society in 1975, but I was beginning to be known internationally and that much she could see. My father lived much longer.

What language did you speak at home?

We spoke Spanish. My parents spoke Yiddish. I never learned Yiddish. My father was very much involved in preserving Yiddish and edited books and collected such books.

Did you experience anti-Semitism in Argentina?

Not to the extent that would have left a bad scar on me.

Do you have heroes?

This is a difficult question. I became interested in science because of the book *Microbe Hunters.* When I read the book, its main characters were all my heroes. Then, gradually, I looked at them in slightly different ways. Paul Erlich was, of course, the father of immunochemistry. I have enormous admiration for his work, even for his mistakes. I talked about it in the 1989 Croonian Lecture ["Antibodies: A Paradigm for the Biology of Molecular Recognition," *Proc. R. Soc. London B* **1990**, *239*, 1–16]. In more modern times, I consider an extraordinary scientist, by all standards, Fred Sanger, in a very strange way. He is a very quiet person but he did and initiated a tremendous amount of work, and his impact in science has been enormous. He had one simple thing in mind — that you have to break the limits of technological capabilities, to work out methods, to do new things. This was his philosophy. He was an absolute pioneer. When he first sequenced a protein, it was not yet clear whether proteins were made by individual amino acids or not. When he did the N-terminal sequences, it was not known that you could actually do such a thing. Once it became clear that the amino acids in proteins were in a certain order, the whole problem of the genetic code became essential. But Sanger was not interested in finding out that, his interest was in breaking the boundaries. He wanted to show that since they exist, you can do sequences. He then went on, in the same way, for methods of doing RNA and DNA. To me, he is the most spectacular experimental scientist. Although he is a quiet and simple person, he was a very inspiring teacher. When you talk to him, you may not think so, but he had tremendous insight into problems.

But then it all ended abruptly when he reached retirement age.

He abandoned it all in a most extraordinary way. I inherited his post, we were joint division heads, and I was supposed to move into his laboratory. I asked when he was planning to empty the laboratory and told him that

I was not in a hurry. He said he would empty it on his retirement, on the first of October. On September 30, he was still doing an experiment. Then I came to his lab on the first of October and the laboratory was empty and he was gone.

Do you go back to Argentina?

During the period of the military junta, I never went back, and used to meet with family members in neighboring countries. Then, after the Malvinas/Falklands war and following the elections, we started visiting again. Now I go very seldom, but only because I find the trip too exhausting. My wife is retired. She is a biochemist and used to work in the Institute of Animal Physiology. Her doctorate was from Argentina and later she got a Doctor of Science degree from the University of Cambridge.

Did your life change after the Nobel Prize?

Some people enjoy publicity but I did not. I feel uncomfortable when I am in the center of attention, when I am being interviewed. But I readily admit that this interview is different, absolutely.

In Argentina, I became a sort of popular figure. because there are not many Nobel Prizes there and also for another reason. After my Ph.D. from the University of Cambridge, in 1961, I went back to Argentina and I stayed for about two years. First I was very happy there. We did good work and published good papers. However, after the military coup, things went bad, and the director of our institute was persecuted. I was head of a division, and four members of my staff were dismissed for no good reason. So I sent my resignation and decided to leave the country. To me it was clear that the minister wanted to get rid of me. He knew that I would resign if they would dismiss my colleagues.

Why did he want to get rid of you?

Because I was a nuisance. All the scientists who were protesting the persecution of the director of the institute were making his life difficult. We were all considered to be communists. Somebody to be called Milstein, obviously a Jew, must be a communist.

Later, when the Malvinas/Falklands war was over and there was a new government and people became interested in the history of the previous years, my letter of resignation got into the limelight in view of my becoming a Nobel laureate as well. I became something like a symbol of what the

César Milstein with his father in 1984 during the Nobel award celebrations in Stockholm (courtesy of César Milstein).

country has suffered. Thousands of intellectuals left Argentina during the military regime, tens of thousands. Many of them have become very prominent in science, so I was only the tip of the iceberg.

> When my wife and I spent three months in Cambridge at the beginning of 2000, we saw César Milstein from time to time. On one occasion he gave me a photograph showing him with his father in 1984 in Stockholm. The similarity was obvious and there was also visible harmony between them. Only upon our return to Budapest did it occur to me that I should have asked him more about his relationship with his parents. So I did this in a letter and here is his response (dated June 22, 2000):

My father came [to Argentina] from the Ukraine when he was 14. He had no family support and became a farm laborer and somehow through his own efforts learned to write and read Spanish. Over the years he tried

a variety of jobs (carpentry, rail-worker, etc.) and became active in cultural activities involving Yiddish libraries and non-religious Jewish organizations, some with anarchist or anarcho-sindicalist connections. Eventually he started as a shop assistant and later became a traveling salesman. My mother was born in Argentine of a family recently arrived from Lithuania. She was a very gifted child and with great sacrifices went to secondary school and eventually became the head teacher of a primary school when still very young. We were three brothers and for both of my parents their highest aspiration was that we all went to University. All of us graduated.

My parents were very strict and I was very rebellious and on many occasions our relations became extremely tense. Somehow the conflicts were kept at a level that never eroded the basic love and appreciation that I had for them. When my parents realized that I was more interested in an academic career than in the professions, they were incredibly supportive. My mother typed my Argentine Ph.D. thesis and my father repeatedly offered me economic assistance so that I could dedicate full time to my research, but I refused (except for the down payment of a mortgage that was their wedding present). I was determined to feel fully independent even though in those days there were no scholarships in Argentina for a research student and I had to do part time work (as did my recent wife) so that we could support ourselves. I dedicated my Argentinean Ph.D. dissertation to them and they (especially mother) became extremely emotional for the gesture. As time went by, they understood and respected my demands for total independence and our relationship quickly lost all the rough edges. They were sad when I told them that we were emigrating to Britain and it was first my mother who came to accept and support our decision.

They were both thrilled and proud to learn of my steady progress and I made efforts to visit them in Argentina at least once a year. Unfortunately my mother died a few years before my first big jump in academic recognition (the Fellowship to the Royal Society). My father however came to London to the ceremony and was — in his tranquil and reflective manner that clearly contrasted with my mother's emotional personality — obviously proud but also somewhat bewildered and amazed that this was happening to him. He also came with me to Jerusalem when I received the Wolf Prize. On that occasion however he could not stop himself when I gave my three-minute speech of thanks. This was when I mentioned that I was a typical example of a Jew of the Diaspora, the beneficiary of the determination of the parents that were willing to make all sorts of sacrifices to see their children in higher education. He jumped from his seat, came to the rostrum (the ceremony took

place at the Knesset and I received the award from the hands of the President of Israel) and to my great embarrassment gave me a kiss! The audience, however, loved it! By the time he came to Stockholm he was more prepared for such occasions and while very moved, he was also very composed when he gave with me a live interview to an Argentinean TV station. By then he had already been interviewed on several occasions in Argentinean TV. He was a natural storyteller and the interviewers loved him for that. Subsequently and on several occasions over the following two years or so he was interviewed for his knowledge of the Jewish immigration to Argentina in the beginning of the past century. He was particularly good at telling the story of a poor Jewish immigrant's struggle in a foreign land, determined not only to raise a good Jewish family but also to contribute to the maintenance of the Jewish culture and the Yiddish language. It gave me great happiness to feel that somehow I was repaying all his own efforts by bringing joy and a new interest to the last years of his long life.

Alfred G. Gilman, 2000 (photograph by I. Hargittai).

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Alfred G. Gilman

Alfred G. Gilman (b. 1941, New Haven, Connecticut) is Professor and Chairman at the Department of Pharmacology, Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, and Regental Professor at the University of Texas Southwestern Medical Center at Dallas. He shared the Nobel Prize in Physiology or Medicine for 1994 with Martin Rodbell (1925–1998) "for their discovery of G proteins and the role of these proteins in signal transduction in cells."

Alfred Gilman received his B.S. from Yale University majoring in biochemistry in 1962 and his MD/Ph.D. from Case Western Reserve University in 1969, where he worked under Theodore W. Rall. Following a postdoctoral stint with Marshall Nirenberg at the NIH in Bethesda and his first professional appointments at the University of Virginia School of Medicine at Charlottesville, he has been in Dallas since 1981.

Dr. Gilman is a richly decorated scientist, and his distinctions include his membership of the National Academy of Sciences (Washington, DC, 1985) and the Albert Lasker Basic Medical Research Award (1989).

We recorded our conversation in his office on July 11, 2000.

First I would like to ask you about the road leading you to the discovery of G proteins and their role and the essence of the discovery.

Looking back, initially we certainly did not appreciate the general significance of the work we were trying to do. G proteins turned out to be vastly more important than anybody could have expected. Actually, that's the way you win a Nobel Prize; you stumble into something that's much more important than you thought it was going to be.

I did my Ph.D. training with Ted Rall; Ted had been working with Earl Sutherland, who won a Nobel Prize in 1971. Everything I did can be traced back to Sutherland and Rall's work and before that to Gerty and Carl Cori (Nobel Prize in 1947) in St. Louis. The question was how do hormones work, and there was a particular interest in glycogen metabolism. Sutherland tried to understand how hormones such as epinephrine and glucagon could raise the blood sugar (glucose). People knew that the glucose came from the breakdown of glycogen in the liver, so the question was how did the hormone, presumably working on the outside of the cell, cause this biochemical reaction.

Sutherland's Nobel Prize was for the discovery of cyclic AMP (adenosine 3′,5′-monophosphate), the first so-called intracellular second messenger. Cyclic AMP is made on the inside of the cell and it then initiates a cascade of phosphorylation reactions that ultimately leads to the activation of phosphorylase, the enzyme responsible for glycogenolysis. This work was very important for a variety of reasons. It put the whole concept of receptors on a firm basis. All of a sudden you could do a biochemical assay *in vitro* that would reveal the activity of a receptor. Before that, the presence of receptors had only been inferred by functional effects, watching a muscle contract or relax, for example. The receptor concept revealed an important mechanism of cellular communication: transmission of information from the outside of the cell to the inside of the cell. And, along with the work of Krebs and Fischer (Nobel Prize in 1992), this mechanism for transmission of information also highlighted the importance of protein phosphorylation reactions inside of cells.

That's where I picked up the game, focusing on this critical reaction in the plasma membrane of the cell and how the information got from the outside to the inside. When I was a student people asked the question of whether the enzyme that synthesized cyclic AMP, adenylyl cyclase, was the same as the β-adrenergic receptor for epinephrine: a single protein that recognized catecholamines at the outside of the plasma membrane and synthesized cyclic AMP at the inside of the plasma membrane. The alternative was a two-component model in which the receptor was separate from the cyclase and they somehow communicated.

Rodbell's work in the late 1960s and early 1970s demonstrated that guanine nucleotides were very important in this process and that GTP (guanosine triphosphate) was an extra, required co-factor for hormonal stimulation of adenylyl cyclase. He suggested that there might be a third component, although he didn't have direct evidence for it.

We started to study the reaction by a combination of biochemical and genetic techniques, and critical to our success was the use of the S49 lymphoma cell line, pioneered by Gordon Tomkins and his colleagues, particularly Phil Coffino and Henry Bourne. These cells had a unique property: cyclic AMP is cytocidal to S49 cells, and so they die in response to anything that stimulates cyclic AMP synthesis. By selecting cells that were resistant to the cytocidal effects of catecholamines, Bourne and Tomkins isolated a mutant cell that appeared to lack adenylyl cyclase. We decided to put the mutant cell membranes back together again biochemically. Those were the experiments that led to the discovery of the first G protein. Elliott Ross and I were able to reconstitute these membranes by adding detergent extracts from other cells that contained adenylyl cyclase; we reconstituted the capacity of the mutant membranes to synthesize cyclic AMP in response to hormones. Of course we thought at first that we achieved this pleasant result by incorporating adenylyl cyclase into the membranes. But, control experiments soon showed us that the mutant cell membranes actually did contain adenylyl cyclase but that the cyclase was silent because of a missing, unappreciated protein. This turned out to be a guanine nucleotide binding protein or G protein that is essential for activation of adenylyl cyclase.

We now know that G proteins are basically switches that can be in two fundamentally different conformations depending on which guanine nucleotide is bound to it, either GTP or GDP. In the inactive or GDP-bound form the G protein is a heterotrimer, with three different subunits, α, β, and γ, tightly associated with each other. The receptor's job is to catalyze exchange of GDP for GTP, and this activates the G protein, causing major conformational changes. The GTP-bound α subunit then dissociates from a complex of β and γ, and both GTP-α and $\beta\gamma$ are then free to regulate the activities of downstream effectors. The G protein switch also has a built in timer. After a certain amount of time the G protein α subunit, which is itself an enzyme called a GTPase, hydrolyzes GTP to GDP. The GDP-bound α subunit can then bind again to $\beta\gamma$ and the cycle is complete.

These observations by themselves were nice, but in the long run we, and many others, learned that G proteins did much more than simply activate adenylyl cyclase. G protein-regulated signal transduction is the most common mechanism of getting information across the plasma membrane, and all animal cells use this mechanism to sense their environment and respond to the many regulatory influences that impinge on them. There are roughly 1500 different receptors that interact with G proteins. The G protein-coupled receptors probably constitute about 2 percent of the human genome.

The G proteins control many different intracellular processes, ranging from sex in yeast to vision and cognition in humans.

The picture that emerges is of a giant switchboard in the plasma membrane of the cell with dozens of receptors, G proteins, and effector molecules that are controlled by the G proteins. There are many convergent and divergent pathways through this maze, and a variety of feedback mechanisms fine-tune the activities of each component. It is an elaborate switchboard, and we still have a great deal to learn about how it works.

Would you, please, give us an example of the role of G proteins in sickness?

There are a few obvious places where derangement of a G protein causes disease. The most important, perhaps, is the disease cholera. Cholera is an infectious disease caused by a bacterium. People acquire cholera by drinking contaminated water. These bacteria colonize the gastrointestinal tract, but they don't invade further; if they did it would be catastrophic. The cholera bacteria produce a toxin, which is a protein with very unique properties. First, it has the ability to get inside the cells. Then, the active subunit of the toxin is an enzyme, and it causes an irreversible covalent modification of one of the G protein subunits, in fact the one we discovered called $G_{s\alpha}$. This modification activates the G protein, and the modification is permanent. You have to degrade the protein and synthesize new protein to reverse the effect, and this takes days. In the meantime, the elevated concentrations of cyclic AMP that are made cause a tremendous outpouring of salt, particularly sodium chloride, into the gut; water accompanies the salt, and the result is a massive diarrhea. People die quickly from dehydration. You can treat cholera simply by infusing fluid back into people as fast as they lose it. Antibiotics can kill the bacteria, but this is a much more expensive cure.

There are also mutations in G proteins that cause disease. Consider again the G protein α subunit that activates adenylyl cyclase. You have two genes that encode this protein. If you lose both of them to mutation, it's lethal. If you lose one of them you have a syndrome called pseudohypoparathyroidism. Patients look as if they are hypoparathyroid. The parathyroid gland is a small gland that's associated with your thyroid gland in your neck. It's particularly important in regulating calcium metabolism and bone structure. Patients who have a deficiency of parathyroid hormone function have a characteristic appearance because of changes in bone structure. Patients with pseudohypoparathyroidism do not actually have a deficiency of parathyroid

hormone but they fail to respond to the hormone properly. These patients also suffer from other deficiencies, including mental retardation. The cause of this disease is the loss of one of the two genes that encode $G_{s\alpha}$.

The story gets even more interesting. Henry Bourne in San Francisco studied a small number of patients (boys) who had a particularly interesting syndrome. They looked like they had pseudohypoparathyroidism, but they also had a condition called testotoxicosis: excessive testicular function, which caused premature puberty. How do you put this combination of things together? You know that pseudohypoparathyroidism is caused by loss of function of one $G_{s\alpha}$ gene. But hyperactivity of $G_{s\alpha}$ would cause testotoxicosis. So there is an apparent contradiction. It turned out there was a simple point mutation (affecting a single amino acid residue) in one of the $G_{s\alpha}$ genes. This point mutation causes a reduction of affinity of $G_{s\alpha}$ for GDP. GDP then dissociates rapidly from the mutant G protein. This is the same thing that an activated receptor does: accelerate the dissociation of GDP from the G protein so that GTP can bind. This accelerated exchange of GDP for GTP causes activation of the G protein. But, the mutation also causes the G protein to be unstable (because of the loss of bound guanine nucleotide); the protein denatures rapidly, and it is more unstable at higher temperatures. Most cells in the body are held at 37°C, and, as luck would have it, the mutant $G_{s\alpha}$ protein is unstable at this temperature. It denatures quickly and its function is lost. So most of the cells of the body behave as they do in a patient with pseudohypoparathyroidism. But the testicles are cooler than the rest of the body! They are at about 34°C. It has been known for centuries I think that you can sterilize men if you bind their testicles in an insulated jock-strap. The mutant $G_{s\alpha}$ protein can survive at the lower temperature of the testicles, amazingly enough, but it is activated because of the rapid guanine nucleotide exchange; thus the testotoxicosis. Medical sleuthing can be extremely fascinating.

Do you continue your work on G proteins?

Yes, but now you pushed my button, because I'm starting a whole new project. While the work in our own lab continues, I am downsizing my individual efforts. I'm trying to launch a broad new program that I'm very excited about. In a cell you have a large number of individual signaling modules — many, many, different modules that control cell functions. What I've done with my life? I've defined how a couple of these modules work. Others have done the same for other modules. We are collectively good

at defining the individual pathways in the cell, but we don't really understand the myriad of interactions between them — how this really complicated network is put together. This is a daunting problem — to understand the properties of the signaling system as a whole rather than just the discrete properties of the individual modules.

Up to now it has been essentially impossible to try to understand how the whole system works, and it is presumptuous to say that I would like to understand it. But you couldn't ask this question before because of grossly incomplete information about all the molecular players. It would've been like trying to put together a large puzzle when you have only ten percent of the pieces. The difference now is the sequencing of entire genomes. Now we have all the puzzle pieces, but many of the pieces still don't have pattern on them and their shape is not yet well defined. We don't yet understand a large fraction of the proteins encoded by the genome. But we now have unbiased approaches for identifying the players and determining what they do.

This turns into a philosophical debate about how to do science. Until now the Holy Grail has been to formulate a hypothesis and to test the hypothesis. But in many cases now we no longer need to be restricted by our hypotheses because all of the pieces are in front of us. We can take each piece and test to see what it does. We can use unbiased methods to detect protein–protein interactions and use one piece to fish out another piece.

For the first time you can write down a plan for understanding how the system works as a whole. But the plan is very complicated and it requires a great deal of effort and thus money. We are going to launch a large multi-disciplinary collaboration involving many scientists in many different universities. We've written a grant application to the National Institute of General Medical Sciences (NIGMS), which is a component of NIH, and it's quite likely that we get funded. We've put together a group of about 50 investigators at roughly 20 universities to work on this problem. It's a different way of doing science. We hope to start in September of this year. It's roughly a ten million dollars a year program. This is occupying all my time and energy at the moment.

So you stayed in science after the Nobel Prize.

The Nobel Prize has given me a visibility that helped to organize this large group and particularly to raise money from the private sector. The

maximum amount NIGMS would give us is five million dollars a year, so it's up to me to raise the other five million dollars a year. The response to our appeal to the pharmaceutical companies has been mixed because we'll make our data available in the public domain, immediately. We will patent nothing. It has also been a challenge to have all the participating universities sign off on the intellectual property. What we'll be discovering is new genes and their functions in mice, and we'll be getting mechanistic information and quantitative information about how information flows through these systems. But none of these things, *per se*, is useful intellectual property. They are tools for acquiring useful intellectual property. We'll be trying eventually to show the pharmaceutical companies where to target drugs and what the exact consequences of those drugs will be.

Have you been involved in biotechnology?

I'm on the board of two pharmaceutical companies — one large and one small. But I haven't been involved in drug discovery myself.

I'd like to ask you about your family background.

I don't know as much about the details of my family background as I should. On my father's side, his parents were Russian Jews, but I don't even know from which region they had come from. My mother's ancestors were from Western Europe. My father was born in 1908. He was the first one in the family to go to college. My mother was trained as a social worker.

You came from an academic family, which is not the most typical of American Nobel laureates.

My father's father ran a music store and my mother's father was a musician. But my father became interested in science and got a Ph.D. in Physiological Chemistry after graduating from college. He held academic positions for all of his life, except during World War II. During the war, he was in the U.S. Army stationed at Edgewood Arsenal in Maryland working on antidotes for chemical warfare agents.

What turned you to science?

It was in the family. The most exciting was the trips to New York City, we lived outside the city, to the Hayden Planetarium. I wanted to become

an astronomer. And then my father would take me to his medical school (Columbia University). In those days there were elaborate teaching demonstrations for medical students, and I used to watch those demonstrations.

You mentioned your dislike of compulsory religion in the Connecticut prep school where you went.

My family was very uninterested in formal religion, my father in particular. He had rejected all formal aspects of Judaism. Compulsory religion only meant that we had to go to church and take a Bible class. Most people went to a Protestant church down the street, and so I did that also. Aside from my lack of interest in religion, it was a terrific school.

After your undergraduate degree from Yale you went to Cleveland.

There was a specific reason. I had done a fair amount of research as an undergraduate. I was interested in medicine, but I wanted to do research. My father was a Ph.D., not an MD, but he felt that the education in biology that you would get in a medical school was very valuable. It was common in those days to get an MD first and then, in addition, to get a training

Alfred Gilman, Senior (1908–1984) (courtesy of Alfred Gilman).

in research, and this is what my father recommended for me. At that point I got this great letter from Earl Sutherland, who was a friend of my father's and who had established this new program at Case Western Reserve University in Cleveland, a 7-year combined MD/Ph.D. program. There was a small group of students; Sutherland recruited every one of us personally. I went there in 1962. Case Western Reserve is an excellent university.

Where did your father get his training?

At Yale University and then he became a faculty member at Yale.

Was it unusual? Didn't Jews have difficulties in getting accepted by Yale at that time? It must have been in the 1930s.

I'm not sure it was unusual; I really don't know. Some say that Jews were not promoted and were discouraged. But my father met his colleague Louis Goodman at Yale and they wrote a textbook together that became the standard in the field; both of them were Jewish.

I would like to ask you about your experience with Marshall Nirenberg.

He is a wonderful person, a shy man. It was interesting working for him. He has a great imagination, he is very creative. He would tend to lead you to problems that required a fair amount of faith to work on. He had a vision of what the problem could become, and it was harder for other people to see what the vision was. We had our disagreements on what I should work on. He loves science with a greater passion than most. He is wholly immersed in science. He's a kind, gentle person.

He has his notebooks where he records his ideas. Did he share them with you?

No.

Do you consider yourself to be his pupil?

Of course. Both his pupil and Ted Rall's pupil.

You also had interaction with Ferid Murad.

Murad and I were graduate students together. He'd also been recruited to the same MD/Ph.D. program. We both worked in Ted Rall's lab.

Ted Rall was the co-discoverer of cyclic AMP but did not share the Nobel Prize with Sutherland. It was the usual story; the younger person working with the more established scientist, and the younger person often does not get the credit he deserves. Rall had been trained as a biochemist in Lehninger's lab at the University of Chicago. Ted was a totally dedicated hands-on scientist. He always had a very small laboratory and may have only had half a dozen graduate students in his entire career. Two of them were Ferid Murad and me.

Would you care to make any comment about the Nobel Prize for nitric oxide?

The discovery was certainly deserving of the prize. Sometimes it is difficult to figure out who should share the credit. The Lasker Prize went to Bob Furchgott and Ferid Murad. They stopped at two. Lou Ignarro, who also made wonderful contributions, was added for the Nobel Prize. Furchgott was totally non-controversial. Murad's work and Furchgott's work proceeded very much in parallel. Murad learned first about nitric oxide as an activator of guanylyl cyclase and a vasodilator. People knew that nitric oxide was a vasodilator, but Murad discovered that nitric oxide worked as a vasodilator by activating guanylyl cyclase and that all sorts of other nitrogen-containing vasodilators, including nitroglycerine, worked by releasing nitric oxide. So Murad created the nitrovasodilator, nitric oxide, guanylate cyclase, vasodilation

Alfred Gilman in 1985
(courtesy of Alfred Gilman).

story. He led the way there without any question in my mind. Furchgott did a beautiful classical series of experiments to discover EDRF (endothelium-derived relaxing factor). Well down the road people figured out that EDRF and nitric oxide are the same. One of the problems of handing out credit for this part of the story is that everybody suspected that EDRF was nitric oxide, but nitric oxide did not lend itself to classical methods of discovery. You never purified the factor, put it into the mass spectrometer and, Eureka, it's nitric oxide. The identification was a more gradual process from hypothesis to strong suspicion, to near certainty, to people finally putting together enough indirect evidence to make it believable.

Does the Lasker Prize also have a limitation at three?

Yes, but this limit has been introduced recently. The year I won the Lasker, 1989, there were four.

Did your Lasker include your co-winner of the Nobel Prize?

No. They left Rodbell out. It was a broader prize; it was for the signal transduction rather than for the G proteins. Michael Berridge, Ed Krebs, Yasotomi Nishizuka and I shared the award, so signal transduction, second messenger generation, and protein phosphorylation were included. Later there was a Nobel Prize to Ed Krebs and Ed Fischer. The Lasker Committee

Co-winners of the 1994 Nobel Prize in Physiology or Medicine, Alfred Gilman and Martin Rodbell (1925–1998) (courtesy of Alfred Gilman).

had ignored Fischer. Thus the Lasker Committee was lumping and the Nobel Committee was splitting. I think the Lasker Committee has become more specific in recent years as well.

In your work on the Lasker Committee, are you trying to anticipate the forthcoming Nobel Prizes?

No, we're trying to lead. It's a very different process. The Lasker is a very large committee with international representation; highly visible scientists who work for a relatively short period of time. The Nobel Committee is a much smaller committee of Swedish scientists, not as well known, who work vastly harder on their decision.

Do you consider the Lasker the next to the Nobel Prize in prestige?

Americans would probably think that; others might not.

What do your wife and children do?

My wife teaches children with learning disabilities. We have three children and none of them went into science. My eldest daughter is an accountant, my younger daughter is a social worker, and my son is an attorney. And I have 2.8 grandchildren, as of now.

There are four active Nobel laureates in this school. Do you ever get together to discuss who should get the next Nobel Prize?

Sure, we sometimes discuss who should, but we mostly try to guess who will. The purpose of the prizes is to call public attention to science. That is critically important because we are dependent on the public for the funding of science. Mr. Lasker was an advertising executive. He knew how to get a message across. The whole point of the Lasker exercise was to gain leverage with Congress to get increased appropriations for science. I've witnessed what it meant to this school to win a Nobel Prize when Mike Brown and Joe Goldstein won their Nobels in 1985. There were philanthropists in this community who were not convinced that this was a top-notch medical school and that it was worthy of their donations. The validation of the quality of the programs in this medical school by the Nobel Committee meant a huge difference — many millions of dollars. Our medical school now has four active Nobel laureates. It's powerful stuff for fundraising. That's the real benefit of the prizes.

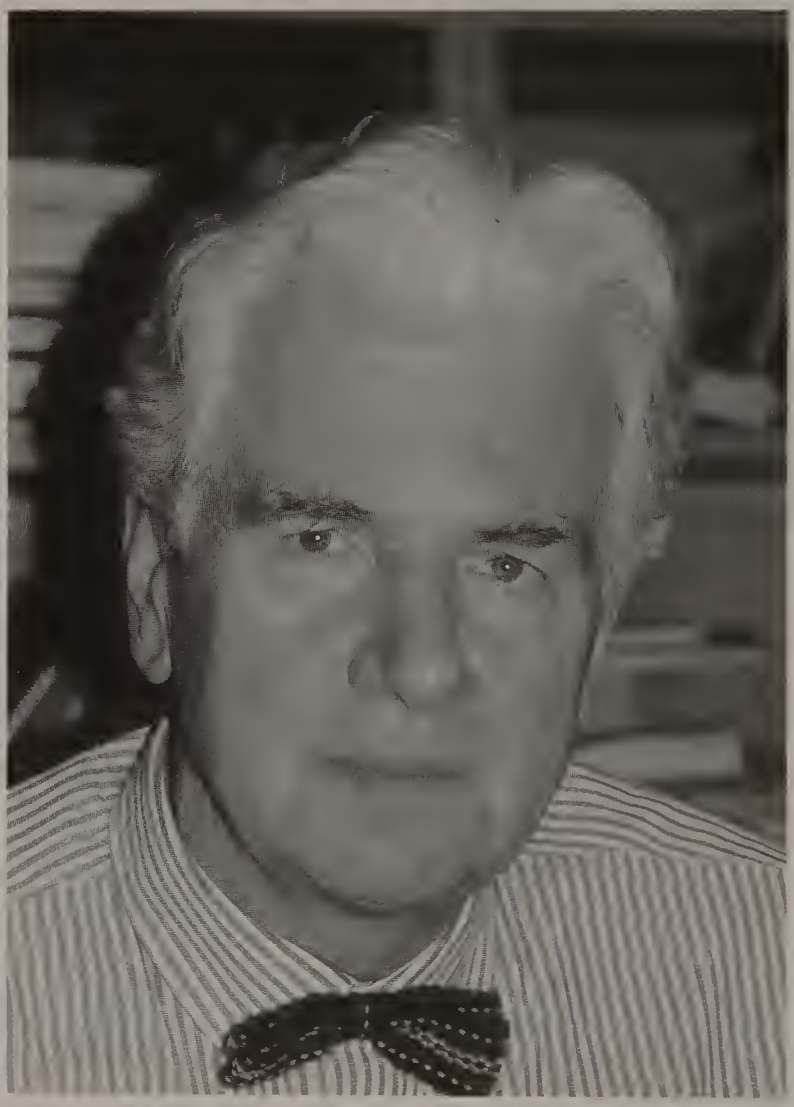
Alfred Gilman lecturing in Stockholm, 1994 (courtesy of Alfred Gilman).

When I was in Stockholm I pointed out that when all other things are equal they should not pass up the opportunity to spread the Prize out as much as possible. Each Prize not given is a lost opportunity to publicize science, particularly in a given locale. Murad, now at the University of Texas at Houston, had a big impact on them in terms of fundraising.

The Prize is also wonderful for the individual. I've jokingly said it's like being given a lifetime depot injection of Prozac.

Any message in conclusion?

I like to urge young people to take up science. It's very hard to find a career where you finish your training and you're then given a franchise for discovery, particularly in the United States. Somebody gives you a laboratory, and while people like to complain about writing grants, it is, in fact, an enormous privilege. You're given a franchise to go to the public and say, "I have my ideas and I'd like you to give me money for them so that I can pursue my own ideas my own way." This country, in particular, is doing a good job of coming forth with that money.



Günter Blobel, 2000 (photography by I. Hargittai).

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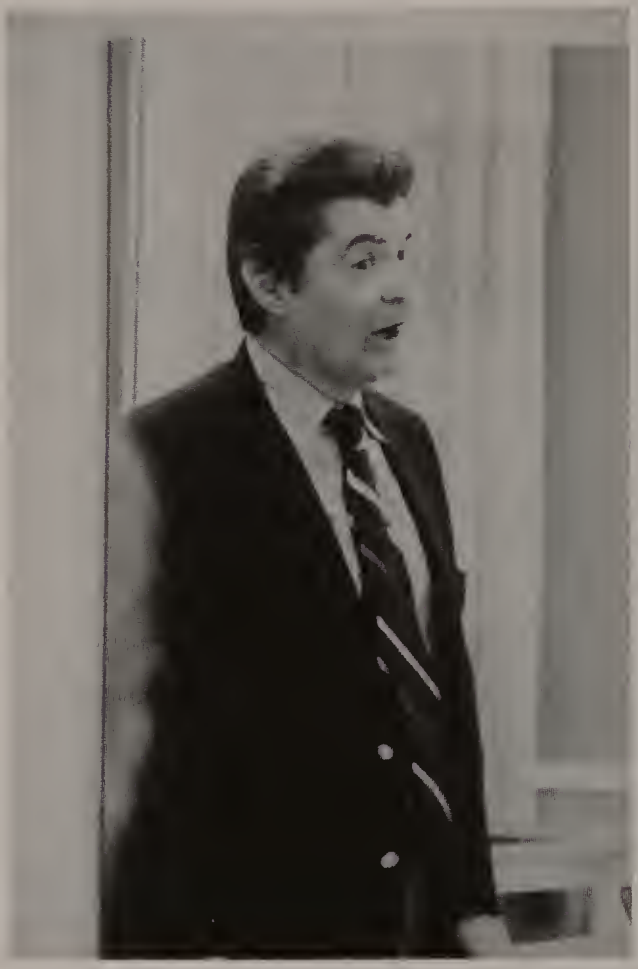
Günter Blobel

Günter Blobel (b. 1936 in Waltersdorf/Silezia, then in Germany) is John D. Rockefeller, Jr. Professor at The Rockefeller University and Investigator of the Howard Hughes Medical Institute in New York City. He was awarded the Nobel Prize in Physiology or Medicine in 1999 "for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell." He received his M.D. degree from the University of Tübingen in 1960 and his Ph.D. from the University of Wisconsin in 1967. He has been at The Rockefeller University since 1967. He is a Member of the National Academy of Sciences of the United States (1983), the Leopoldina (a German science academy in Halle; 1983), the American Academy of Arts and Sciences (1984), and the American Philosophical Society (1989), among others. He received the Gairdner Foundation Award in 1982, the Warburg Medal of the German Biochemical Society in 1983, and the Albert Lasker Basic Medical Research Award in 1993, just to mention a few of his many decorations. In 1994, he founded the "Friends of Dresden" Society and has served as its President ever since. We recorded our conversation in Dr. Blobel's office at The Rockefeller University on May 9, 2000.

First, I would like to ask you about your Nobel-Prize-winning discovery, in particular, about going from the signal hypothesis to the evidence.

It started with a simple question of how the secretory proteins get across the endoplasmic reticulum membrane, which is just the beginning of the so-called secretory pathway. The secretory pathway was discovered by George



George Palade (b. 1912, Nobel Prize in Physiology or Medicine for 1974, shared with Albert Claude and Christian de Duve, "for their discoveries concerning the structural and functional organization of the cell") (photograph courtesy of Edit Ernster).

Palade who got the Nobel Prize in 1974. He found that secretory proteins cross the endoplasmic reticulum (ER). They get into the lumen of the endoplasmic reticulum and by vesicular carriers are transported by fission and fusion events into downstream Golgi compartments and the plasma membrane. This is the secretory pathway. Initially we were interested in how the proteins get across the ER membrane, why is it only secretory proteins that get across and why not other proteins, and what are the selection mechanisms? These simple questions then led to a much larger question of how proteins, generally, are distributed in the cell? Mechanisms similar to those secretory proteins turned out to work for the distribution of essentially all proteins. It is especially important that these mechanisms also account for putting a membrane protein properly into the membrane. Opsin, for instance, has seven trans-membrane segments, an amino terminal that is trans-located and a carboxyl terminal that is not trans-located. All of the millions of opsin molecules in the retina have to be stitched into the lipid bilayer exactly the same way; otherwise they cannot function

chemically. The program of stitching the protein into the membrane is again determined by sequence elements. So our project expanded beyond the question about how a protein traverses the membrane. We ended up understanding how the cell organizes itself.

The machinery decoding the sequence element is very interesting. For instance, the protein-conducting channel in the endoplasmic reticulum is opened by the signal sequence. It is not just a tube but it is a scanning device, which reads what goes across and can also open laterally to the lipid bylayer.

What is the channel made of?

It is made of integral membrane proteins.

Does this mean that the same protein would not get through in a different conformation?

It's not just the signal sequence but you need a whole accessory machinery that decodes it. For instance, take the signal sequence of the secretory protein, which happens to be hydrophobic. It would fold up in such a way that it would be in the interior of the folded structure. Then its information content would be lost. However, the cell has developed a particle, which we identified and called the signal recognition particle, SRP, and it consists of RNA and six proteins, forming a ribonucleic acid-protein complex, which can bind to the large ribosomal subunit. It is a long cucumber-shaped particle. At one end it has a protein, which can recognize the hydrophobic signal sequence and can bind it. In its crystal structure you can see a groove, which can accommodate hydrophobic amino acids so you can protect the hydrophobic amino acids and segregate them from the rest of the chain. Without that particle the chain would fold up and lose its information content. Once you have the signal sequence of the chain, you now have to do targeting because there are many membranes in the cell. In the endoplasmic reticulum, there is a receptor that recognizes the SRP. This receptor consists of two subunits and can bind the entire complex and that completes the targeting step.

The signal sequence has yet another function. It serves as a ligand to open the protein-conducting channel. This is why you have to keep it separated from the rest of the chain and prevent the folding and the hydrophobic portion getting into the interior of the molecule. Then you have to release the signal sequence from the signal recognition particle

in order to present it to the protein-conducting channel where it binds and the channel opens. This process is not yet well understood.

We do know, however, that there are three GTPases[1] involved. Eventually, the signal sequence is released from the SRP but only if it is close enough to the channel; it gets bound to the channel and the channel opens. In the meantime the ribosome also releases a translation arrest. The SRP not only recognizes what comes off the exit site of the large ribosomal subunit but can also influence the peptidyltransferase activity in the large subunit. When it binds, it slows down translation until the SRP is released and that only occurs when the signal sequence binds to the protein-conducting channel. This prevents the synthesis of the remainder of the chain that would entangle everything. Once you open the channel, the translation continues and the GTP hydrolysis provides the energy for translocation. The channel will read what is going across; the chain is going across in an extended configuration. It will open laterally when there is a hydrophobic trans-membrane segment passing through the channel. So membrane proteins have a signal sequence to open the channel, in one dimension, across the main chain and another hydrophobic segment, termed a stop-transfer sequence, which can open the channel laterally. The stop-transfer sequence is then displaced into the lipid bylayer where it becomes the trans-membrane segment of the integral membrane protein. So it's a very complex process, which took us many years to figure out. Alternative hypotheses were that the signal sequence would spontaneously partition into the lipid bylayer and the free energy from this partitioning would be enough to get the rest of the chain across.

Throughout these years there must have been some decisive moments.

We started out with a hypothesis for which there was no evidence.

Where did the hypothesis come from?

We proposed it with David Sabatini when we were postdoctoral fellows. We thought that each secretory protein may have a signal sequence at the amino terminal, which would specify them to go across the endoplasmic reticulum.

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[1]GTPase: enzymatic activity to hydrolyze GTP [guanosine triphosphate] to GDP [guanosine diphosphate].

Was sequencing available by then?

No, only a couple of proteins had been sequenced. When we looked at the amino termini of various proteins, there was nothing common there but this didn't deter us. We felt that the sequence might be a transient element and, as it turns out, the sequence is then removed by an enzyme, which we call the signal peptidase, and which sits on the other side of the membrane. As soon as the signal reaches the other side of the membrane, the enzyme cleaves it. There are some exceptions to that but the signal is usually removed. Therefore, if you look at mature secretory proteins you won't see anything because the signal would've already cleaved off.

Was this a direct continuation of Palade's work?

Yes. It was a molecular analysis of the first reactions in the secretory pathway, the beginning of molecular cell biology. Palade and coworkers used the electron microscope, cell fractionation, and radioautography to follow a secretory protein in the cell. They showed that the secretory protein somehow ends up in the endoplasmic reticulum, shortly after its synthesis. In the two papers for which I got the Nobel Prize and which were published in 1975, we reconstituted the entire process, from isolated components, in the test tube. This allowed the biochemical analysis of the events. Palade actually reviewed and corrected these two manuscripts. I still have the original manuscripts with all of Palade's handwritten corrections, page after page, "I would say this, I would not say that, I would do another experiment, Wonderful, Great," and so on.

His name is not on the papers.

It's not but he was a very great mentor.

Was this the single most important point in your career?

No, it wasn't but it allowed us then to do the biochemical analysis. It was for the first time that a very complex sequence of events was reconstituted faithfully in the test tube. As we now know there are many reactions in this system. The detailed analysis took 20 years. The first thing we isolated was the signal recognition particle, which recognizes the signal sequence. This was a ribonucleoprotein particle, which was totally unexpected. This happened in 1980, so it took us five years to get to that point.

There was much opposition against our ideas. There were people saying that the information was in the folded protein, not in the signal sequence.

Was your idea too new?

It looked too simple. But the opposition was very good for me even though it gave me a lot of headaches.

Did you experience difficulties in publishing your papers?

We did, but this is common. One of our most important papers ever, the paper that I'm proudest of, a combination of biophysics and electrophysiology, which demonstrated the existence of a protein conducting channel, had such a fate. The editors of *Science* tortured us because they had terrible reviewers. One of them declared that our paper was of no interest to anybody. Another said that it was all wrong, it was all artifacts. The manuscript went back and forth for three or four months. Finally they said they would publish a thousand words or something like that and I said, forget it, and I went to another journal.

Which was it?

We published it in *Cell.* The paper was accepted in 24 hours and appeared 4 weeks later.

Apparently your opposition had melted away and you won the Nobel Prize.

Although there were many other people who contributed to the field we carried it through, from the initial hypothesis to the reconstitution of the cell-free system and the discovery of SRP and the SRP receptor. Then we used electron microscopy and showed what the channel looks like. So our work went all the way. Of course, you may ask whether to find out what happens to the secretory protein should be distinguished with a Nobel Prize? It turned out that we also learned about membrane proteins, how membranes are made, how mitochondria are made, how chloroplasts are made, how the cytoplasm communicates with the nucleus. Our findings turned out to be relevant for a large number of proteins, for the majority of proteins. Some of them have not only one "topogenic" sequence element but several. All these sequence elements have to be decoded by a machinery. There is a huge amount of cellular activity devoted to making sure that

the proteins go to the right address. Some proteins live for a very short time, some live for a long time, you can't repair proteins, they must be made constantly anew. Proteins are damaged all the time and since they cannot be repaired, unlike DNA, they are degraded and replaced. Proteins only function if they are in the proper context, therefore it is very important to put them into these contexts.

You came from Silesia, which is Poland today but you are German and grew up in Nazi Germany. How did this effect you?

I was eight and a half years old when the war was over. The only memories I have of the unpleasant period of the Nazi time in school were that every morning we had to greet the flag. I was tall for my age but had no muscles; the ceremony lasted for 15 minutes and lacking muscles, my salute was slack, and the teacher hit my hand with a stick. I found it very disgusting. I knew that my parents were not sympathizers, they were against the regime.

When did you leave Silesia?

We left at the end of January 1945. My mother was from Saxony and she had relatives there. It was rumored that the Americans and the Russians would meet at the Elbe River so people were trying to get west of the Elbe. My father was a veterinarian and had a car. He wanted to take her mother with us who lived nearby but she refused to leave. After the Russians came she was killed and thrown into a river. The rest of the family escaped and we finally stopped west of Dresden. This region later became part of the Russian occupation zone in exchange for a section of Berlin. Initially, all of Berlin was occupied by the Russians. So where we stayed became part of East Germany, the DDR.

When did you leave the DDR?

I left in 1954. I took a train, before the wall was erected.

The rest of the family?

We were eight children, my older sister had been killed during the war. We were not allowed to study in East Germany because we were capitalist elements. A veterinarian was considered to be a member of the bourgeois capitalist intelligentsia. I could've become a baker, a plumber, or a construction worker, or something like that. The universities were supposed to be for

the children of the workers and farmers. I completed my secondary education in Freiberg, a beautiful old town between Chemnitz and Dresden, which was not destroyed in the war. It has an old and famous university for mining and metallurgy. This is the *Erzgebirge* region. My father was working as a veterinarian in Freiberg.

When I left East Germany, I became a medical student in Frankfurt. Then I went to other places continuing my studies in Kiel, Munich, and Tübingen. Migration was encouraged in those days. It is no longer common. I graduated in Tübingen in 1960.

How did you become interested in science?

I was always fascinated by science. We had very good teachers in medical school, particularly in physiological chemistry and in anatomy. The lectures were fascinating in the old German academic tradition. They also emphasized what we didn't know yet. Suddenly there was a whole universe of the unknown! I realized that if I would go into medical practice, I would never be able to explore this universe of the unknown. So I became interested very early in research but I completed medical school and my internship. I had a brother here in the United States who had a similar idea. He was a veterinarian and eventually he became a Professor of Bacteriology at the University of Wisconsin. He was an influence on me and organized for me to work with Khorana in chemistry or Van Potter in biology. I was a little scared of chemistry, opted for biology, and got my Ph.D. there.

May I ask you about religion?

Obviously, I'm not a fundamentalist. Einstein once said, "Religion without science is blind and science without religion is lame." But religion in an Einsteinian sense is a system of order, and has nothing to do with fundamentalism. There is also a cultural aspect to all religions. Religious inspiration has brought many problems for man but it has also created many beautiful things.

You donated the Nobel Prize money to the Friends of Dresden Foundation. Was this on the spur of the moment?

I'd thought about it before, if it ever comes, this is what I would do. My wife was very enthusiastic about it. The Synagogue in Dresden was burned down on *Kristallnacht* by the fascists and they are building a new synagogue. So I gave money to both the Synagogue and the *Frauenkirche*

proportional to the construction costs. I'm going to Dresden on June 21 to be present at the laying of the foundation stone for the Synagogue, and to hand over the checks for the Synagogue and the *Frauenkirche.*

It was not my intention to single out the bombing of Dresden and I don't want to point fingers at anybody, or get involved in the question of why was this done and so on. Horrible things happened but we should also look forward and do something constructive. Jewish life contributed greatly in Germany to the culture of the country and it was wiped out by an insane regime. We have to make an attempt to revitalize Jewish life. One obvious way is via the Synagogue even though I am not a very religious person. The Jewish population in Germany is fast growing because of the influx from Russia.

You were a student in Germany in the 1950s. According to Benno Müller-Hill, there was a cover-up of the past in German university life.

In East Germany where I lived until I was 18, we were taught that the concentration camps were where primarily communists were killed; the Jews were hardly mentioned. Later it changed, but while I was in East Germany I didn't know about the six million Jews killed in concentration camps.

Günter Blobel
(courtesy of Günter Blobel).

I saw movies about concentration camps for the first time in the United States. That was not shown in East German television or radio programs or schools at that time. We were totally uneducated in that. This has changed dramatically since.

Do you think that bombing Auschwitz and the railway lines to Auschwitz might have helped?

Auschwitz was a tiny little town and I'm not sure if the Allies knew to the full extent, what was going on there.

It was a huge complex of many camps and there is evidence today that the Allies knew, what was going on there.

But the railway lines were probably not major railway lines.

The enormous progress of molecular biology and biotechnology has prompted discussions of the possibility of "improving the human race." How do you feel about this?

"Improving the human race" is an ill-defined term. We know what Hitler meant by it. On the other hand, you could also do genetics counseling. Suppose you carry a defective gene. You could do *in vitro* fertilization and test one cell of the eight cell embryos and implant only the embryos that are healthy. When there is new knowledge, it must be sorted out. It's not just the responsibility of scientists but of lawyers and other professionals. Science only creates new options.

Do you know that thousands of brains of mental patients killed in the Nazi times are still being stored in Germany?

I've heard of that.

Shouldn't they be buried?

Yes.

Do you patent your discoveries?

We have a few patents here and there, for trivial things. I did not patent my most important discoveries. If we had patented them, I could have built the *Frauenkirche* and the Synagogue all on my own money.

Any regrets?

I've never been interested in money. If I make money, I give it away. We live a simple life. I get great pleasure from simple things, just looking at a tree, for example. I don't need yachts in the Bahamas or an apartment in Paris for that.

Do you have hobbies?

Music, architecture, and painting.

Who in music?

Bach, Mozart, Beethoven, Schubert, Schumann, Strauss, Wagner, Mahler, Bartók, and many more. I used to play the piano.

Architecture?

I've always been interested in structures, in what you can do with the basic elements, the column, the arch, and the dome, the variations, the proportions, and the spaces that you can create. This is also the basic tenet of biology, building a tremendous variety of structures from basic building blocks.

Who are your heroes?

Scientists, composers, and architects. Mendel, Virchow, Darwin, Palade, Crick, and Watson, an endless list.

What do you read?

I don't have time to read as much as I would like.

You received the Nobel Prize half a year ago. Did it change your life?

It has changed my life in many ways. I have interviews like with you, which I wouldn't have had before. I'm doing them because it's important to give the public an idea about science. This is why I have accepted many television appearances and I've learned to explain my thoughts in simple terms. I consider this my obligation.

Has your wife's life changed?

Her life has changed less but we have more social events and more dinner invitations.

Your wife owns a New York restaurant. She must be busy with it in the evenings.

It's a very competitive business. That has been good for me because I could stay in the lab in the evenings.

Do you live a sizzling intellectual life? You are at The Rockefeller University and you are its 20th Nobel laureate; few countries have so many Nobel laureates. You live in New York City, which itself is a thrilling experience.

New York has an incredibly rich palette of things to do. We do something almost every week. We just saw *Copenhagen*.

How did you like it?

It's one of the better plays but still not totally satisfactory. Did you see it?

In London.

Many of the conflicts you could've discussed are not really discussed. It is interesting but not that stimulating. Did you like it?

I liked the play but it has always bothered me that Heisenberg went to see Bohr and did not make clear his stand on anything. He was, whether he liked it or not, a representative of a power, which was occupying Denmark. Once he decided to go, he should have made his purpose clear.

He shouldn't have gone in the first place. At times the play resorted to banalities.

How do you feel about Austria?

Haider is an opportunist of the worst type, but the whole affair is exaggerated. How about Le Pen in France?

They are in the government in Austria.

But are they doing anything bad? I think it's an overreaction about a few astute opportunist people who are given more publicity than they deserve.

How do you compare German science and American science?

German science is as good as American science, except that Germany is a much smaller country but they have excellent people. Germany is the strongest country in Europe in science.

Not Great Britain?

No longer. The British did not invest in infrastructure. In Germany there are many institutes. The salary structure for English scientists is also very poor and many have left.

Would you have a message?

For young scientists, that they should pursue their ideas even if there is opposition, as it was in my case. For physicians, that they should all spend a year or two working on a scientific problem. They should spend some time in science to understand how little we know, and when they treat a patient, how many outcomes there may be.

George K. Radda, 2000 (photograph by I. Hargittai).

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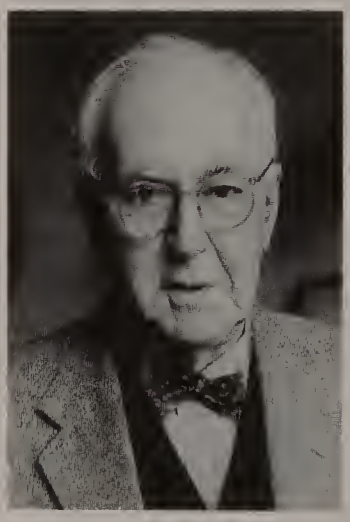
George K. Radda

George K. Radda (b. 1936 in Györ, Hungary) is British Heart Foundation Professor of Molecular Cardiology at the University of Oxford and he is the Chief Executive of the Medical Research Council (MRC). After having started his university studies at Eötvös University in Budapest, he left Hungary after the 1956 Revolution and graduated from the University of Oxford in chemistry (B.A., 1959; Part II Chemistry, Class I, 1960; D. Phil. and M.A., 1962). He did postdoctoral work at the University of California at Berkeley and has held various positions at the University of Oxford since 1961, rising to his present position in 1984. Professor Radda has been associated with Merton College, Oxford, since 1961, becoming Professorial Fellow in 1984. He was elected Fellow of the Royal Society (London) in 1980 and Member of the Academia Europaea in 1999, and he has won numerous awards and distinctions. He has also held various science policy making positions, becoming Chief Executive of the MRC in 1996. We recorded our conversation at the MRC headquarters in London on February 11, 2000.

If we may jump right into the middle, in 1947, Lawrence Bragg turned to the then Head of MRC, Edward Mellanby and asked for support for the work on protein structure in the Cavendish Laboratory. Bragg wanted to see Perutz's work put on a permanent basis but, I guess, this was a rather new initiative for MRC. When MRC gave its support it was the seed of what since has become the Laboratory of Molecular Biology in Cambridge. My question is whether you receive such "outrageous" proposals today, and if you do, are you in a position to support new

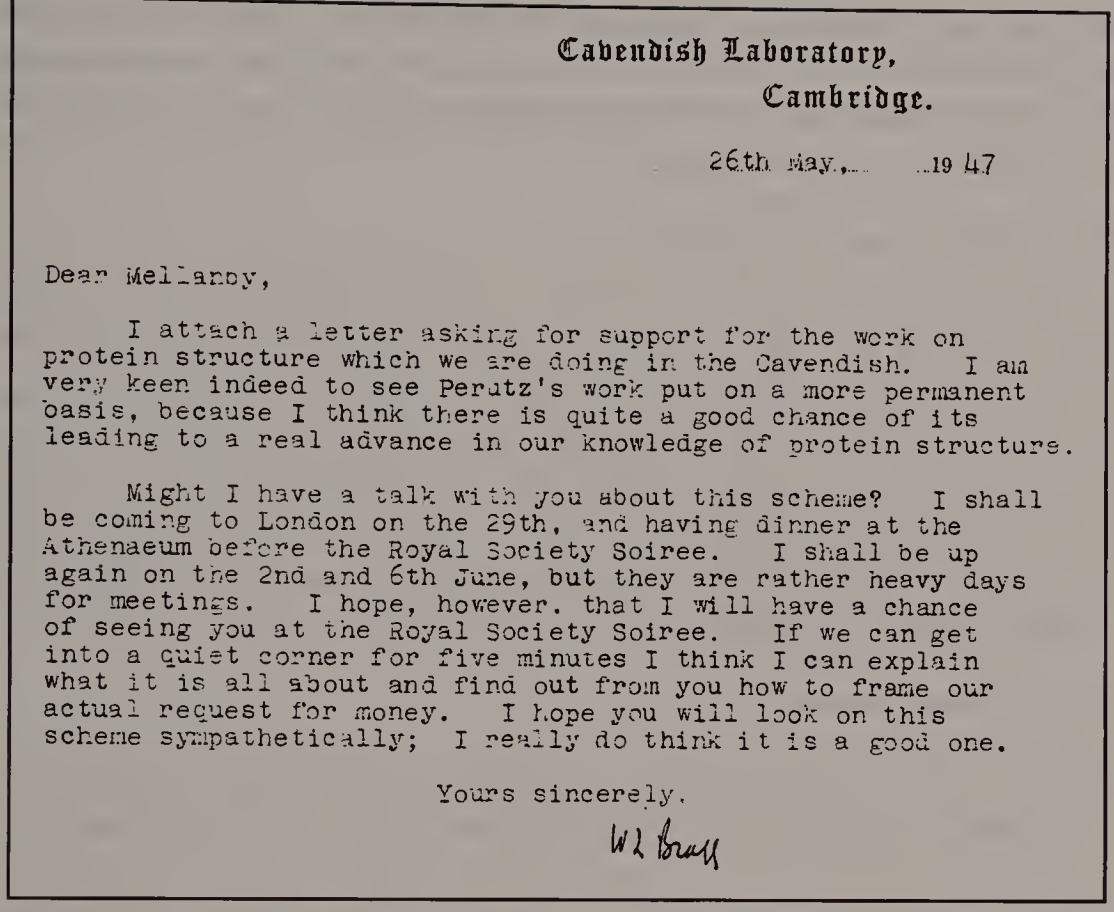
projects that may carry considerable risk in the feasibility of their medical applications?

We are in the position to support risky projects and we are trying to encourage them. Fewer and fewer people come forward with risky projects simply because they are under the impression that those are not funded. It is true that when you have peer-reviewed programs that depend on other



Edward Mellanby, the Head of the Medical Research Council (MRC) when its support for the work on protein structure in the Cavendish Laboratory was initiated (courtesy of the LMB Archives).

Lawrence Bragg (Nobel laureate in physics, 1915) who in 1947 asked the MRC to support the work on protein structure by Max Perutz in the Cavendish Laboratory (courtesy of the LMB Archives).



Cavendish Laboratory,
Cambridge.

26th May, 19 47

Dear Mellanby,

I attach a letter asking for support for the work on protein structure which we are doing in the Cavendish. I am very keen indeed to see Perutz's work put on a more permanent basis, because I think there is quite a good chance of its leading to a real advance in our knowledge of protein structure.

Might I have a talk with you about this scheme? I shall be coming to London on the 29th, and having dinner at the Athenaeum before the Royal Society Soiree. I shall be up again on the 2nd and 6th June, but they are rather heavy days for meetings. I hope, however, that I will have a chance of seeing you at the Royal Society Soiree. If we can get into a quiet corner for five minutes I think I can explain what it is all about and find out from you how to frame our actual request for money. I hope you will look on this scheme sympathetically; I really do think it is a good one.

Yours sincerely,

W L Bragg

W. L. Bragg's note to E. Mellanby, dated May 26, 1947 (courtesy of the LMB Archives).

scientists saying, this should be supported, they are very much more conservative than a single individual can be. But, yes, we encourage long-term and risky projects and our structure, this unit/institute structure, does allow us to do that. First of all it allows directors the freedom to start up things and they don't have to go for extra money because they have enough money in the budget for risky components of their work. Also, because there is long-term commitment, your job and your next grant is not so dependent on publishing every year.

The Rockefeller University used to operate in such a way but they no longer can afford it. What is the trend at the MRC in this respect?

Our budget has been increasing in the last two years quite substantially and the expectation is that we'll certainly be able to maintain our current activities if not more. We are government funded, dependent on public

funds but independent in our decisions of how we use the money. We have both the freedom to look at new programs and close down old ones but at the same time we have reasonable stability in terms of what we can expect from the government.

Who oversees your operations?

I oversee the whole of MRC operations and I am responsible for the total MRC operation and the way our budget is spent. The level above me is the Department of Trade and Industry who give the money and have an Office of Science and Technology. They oversee the science budget but once we have got our funding it is my job to spend it in a wise way and for the best scientific purpose. So my job is a scientist's job, not a job for an administrator. I am attaching a great deal of weight that I should remain a scientist while I do this job.

What is your research?

My research has had a fairly wide-ranging set of activities. I started off as a chemist and changed into biochemistry immediately after my Ph.D. My research has been going from initially looking at the mechanism of enzyme regulation in the late 1960s, early 1970s to issues like how can what we learned about enzymes and proteins in solution in isolation, be translated into their function in the cell and *in vivo*. So I started to build up the complexity of the systems that I studied from single enzymes to enzyme interactions, mitochondria, the whole cell. Then came really the crunch in the work when we had done as much as we could on looking at the activity of the regulation of a particular enzyme, it happened to be the enzyme phosphorylase. I interacted with people in Debrecen, Hungary, in this study in those days. We knew how this enzyme was controlled in solution and we wanted to find out how this behaved in the cell, whether it was the same or not the same. We started to think in the mid-1970s, how can you look at chemical events and structures and interactions within an intact cell or an intact organ. We'd done a lot of work with nuclear magnetic resonance (NMR) on structures and on solutions and somebody suggested to look at the cell, to use NMR for looking at the inside of the cell. In 1974, we were the first group that showed that this was possible. We took a piece of muscle and put it inside the NMR spectrometer, and identified some of the chemical signatures in the cell, molecules like adenosine triphosphate (ATP). We could actually look at the bioenergetic consequences

of enzyme reactions, mitochondrial function, and so on. The very first experiment we did on the muscle told us that what we learned about the solution behaviour of the enzyme phosphorylase did not apply to what went on in the cell. So we said that was OK, can we actually take this forward? Since 1974, since the first paper we published on this, we built up the NMR approach of looking at perfused organs. I've done most of my work on the heart, looking at the relationship between cardiac function and cardiac bioenergetics. Then we hit on the idea that if you can look at an isolated heart, why couldn't you look at the heart inside a living animal. We thus developed the technology to look at the biochemistry of living animals. We then took it all the way to humans. From the 1980s, I had the first clinical set-up of what is now called magnetic resonance spectroscopy (MRS) to study clinical problems in the light of the basic biochemistry that we were doing in parallel. That was my most productive and most exciting period when I ran a major clinical unit with lots of doctors looking at patients. We studied three or four thousand patients, lots of diseases, heart disease, weight disorders, trying to understand the basic underlying biochemistry associated with the disease. We had model studies on animals, on isolated tissues, and on cells, to link it all up. That has been my major effort. That work was done in Oxford; I was head of the Department of Biochemistry and head of an MRC Unit of Clinical and Biochemical Magnetic Resonance at the hospital in Oxford. I worked on two sites, with a clinical and with a basic group. I had to give up my MRC Unit when I became the Chief of MRC because that would have been a conflict of interest. I still have a Chair in Oxford supported by the British Heart Foundation; I am a Professor of Molecular Cardiology.

Did you coin this term?

Yes. It means to look at molecular events inside the intact heart. We look at the way substrates are utilized, the way energy is produced and used. You can study turnover events, you can study mitochondrial function in the intact heart, look at the rates at which ATP is synthesized and at which it is used, what controls it, how it is linked to other chemical processes, like the use of glycogen, and you begin to be able to put together the whole biochemical basis of a contracting heart.

When Linus Pauling introduced the term "molecular medicine" decades ago, he was almost ridiculed. It was a long way to molecular cardiology.

Or take Aaron Klug's Nobel lecture when he anticipated combining molecular science and cellular science. Today there are journals combining these terms in their titles. How do you see the broader perspective of this development?

This science has exploded and exploded partly because we will have access to all the molecules that are present in the cell in some form or other, through the sequencing of the human genome and getting the whole genetic information. In order to understand what these molecules do in the first instance, you have to link up the basic studies of the isolated structural side of that molecule with functional studies in the intact organ. That's the span that you have to cover, and that is now in front of us. The next ten to fifteen years are going to be enormously exciting in biomedical research because the way we are looking at cellular function will be completely transformed.

Suppose there was a discovery in an MRC unit 30 years ago, and the discoverers wanted to patent it, MRC was not encouraging it.

In those days, probably not.

This has changed radically.

Yes.

I would like to ask you about this change and about the proportion of MRC income from patent royalties in comparison with your total budget.

First of all, why it has changed? It has changed because the opportunities are now much better to exploit the scientific discoveries. Also, the mindset of the younger people has changed. The old professors, and I put myself in that category, when they were young researchers, were discouraged by the university to interact with industry; it was something not very clean. The world has changed. The young students in the lab constantly think of how we could exploit what I am doing now. It is the people who want to do it and that is one of the reasons why it has changed. That means that organizations like us had to respond to that; in many ways we led the way making sure that it could be changed. We have set up a very powerful group of people for technology transfer and the MRC has 12–14 spin-off companies. We were the first one in this, Celltech,

a very large company now, was an MRC spin-off. We have many others. We also have many licenses, something like 240. This is now becoming more and more important. The government encourages it now, the universities want to do it, and the individual scientists want to do it. Everybody is for it. This is the answer to the first part of your question.

How much income it generates? It is just beginning to bring us major income. At the moment we are talking about seven million pounds per annum directly. Our total budget is about 340 million pounds per annum at the moment. So it is a small part of our total budget but this is profit, if you like, income that we can use. We pay from this for the whole of the technology transfer operation. The discovery that is bringing us most money is in humanized antibody. You'd talked to César Milstein; his discovery was not patented, and everybody regrets that, I suppose, perhaps with the exception of César Milstein. He is not one of those chaps who are interested in that. Greg Winter who has followed up from César in the LMB set up a "Catalytic Antibody Technology" company, which is floating, and many of his patents are now being used for actual treatment. So there are now humanized antibodies for cancer treatment and various other things and that is bringing us income. That kind of income is going to increase enormously.

You said that even young students in the lab have an eye on application and the corresponding income. Is this good?

It is good up to a certain extent. The danger is that you only do work in order to have that. There is still a reasonable balance here. In the United States, Harold Varmus, the former head of the National Institutes of Health talked about this problem publicly. He was very concerned that almost every postdoc in the United States had a spin-off company and that the driving force for science was not the right one. We haven't reached that stage and I hope we will never reach that stage. What we are trying to encourage within our organization is that the scientist's job is to do top class science and we are here to help the scientist if the discovery could be exploited; at a certain stage there can be a choice. The scientist can stay in top class science and we will make sure that there is personal income from the discovery because we will set up the company or do the technology transfer. But if the scientist wants to go the company way, then he has to move out of science. What we don't want is scientists driven, in our institutes and units, by commercial aims.

How much is your support dependent on anticipated applications?

We look at the scientific quality, the timeliness only. We ask the question from the applicants, do you see a potential commercial application, but it has very little effect on the judgement of whether we support it or not. We are very firm on the quality of science.

As your American counterpart is the National Institutes of Health (NIH) although it is a much larger organization with a much larger budget, is a comparison possible?

NIH has 18 billion dollars and they have got another billion this year. We have 350 million pounds. They are a huge organization. As it happens, we have very good relationships with the NIH and I am very glad about that. My colleagues at the NIH regard U.K. science as very important for the world of science and they have high regard for the way we at MRC do things. This is very pleasing. It also helps that I am a scientist in their eyes. Many of the people who work at NIH used to work with me; some of their top people had been in my lab so they know that we are serious about science and they know how we work. I don't feel uncomfortable with them. OK, they can always outnumber us but we are more cost-effective. As regards quality, if you take the top institutions in the United States, there is no difference but if you take the average quality of science you get for their 18 billion dollars, the quality is not as high as the average quality of science you get here for our money. I'm speaking about the biomedical field and what I am saying is not necessarily true across the science activities in the United Kingdom. We've had a long tradition; we are one of the oldest government supported organizations for research, independent of government. MRC was set up at the beginning of the last century. There is a two-volume book by A. Landsborough Thomson on the history of the MRC [*Half a Century of Medical Research*, Volumes I and II, Her Majesty's Stationery Office, London 1973 and 1975]. It was interesting how it was set up because it was set up to solve the problem of tuberculosis (TB). The government wanted a group to look at TB. They discussed that with the people who were setting up the predecessor of MRC, which was called the Medical Research Committee. Those people had the foresight to say to government, if you want us to solve TB, you can't expect us just work on TB, you have to accept that you have to do basic scientific investigations in all fields of medicine and medically related science. So the initial charter of the MRC was such that

it defined medical research in this broad sense. We have been able to stick to that. We have units and institutes and the Laboratory of Molecular Biology (LMB) is one of them that is not dealing directly with diseases, rather, where people are doing fundamental, outstanding, world-class, leading science. And that will lead to solutions of diseases; the antibodies are a very good example. We have had that tradition within the Medical Research Council, which had a major influence on the tradition of U.K. biomedical research. Until recently we were the only funders of medical research. Now, of course, with the Wellcome and quite big charities here, we are not. But we have led the way and that is why we are in such a strong position.

How many Nobel Laureates have been supported in their research by the MRC?

It is 16, 10 of them in the LMB.

How much weight do you give to this?

It obviously has a tremendous importance to see these people winning these prizes. It is obviously good to show but it is one out of so many hundreds. There are lots of good scientists about who could equally win these prizes. I am glad to say, we don't have the same sort of pressures here as in the States where if you are a leading scientist, you think that you are in for a Nobel Prize and people get disappointed year after year and their institutions get disappointed. We don't look at it that way; we are obviously delighted by a Nobel and there are many other prizes but in the end it is what science you produce that is what is going to matter. The prestige of the Nobel Prize is out of proportion because there is so much good science.

Salvador Moncada did not get the Nobel Prize for nitric oxide and many were disappointed that he was not among the winners for he had done truly pioneering work. He is British but he is originally from Honduras. Does this make any difference? Would the British lobby for him the same way as for anybody else?

He had a lot of support for that from the United Kingdom. It was not for the lack of support from here. Take my own case. I am very comfortable in British science and I am leading British science and I wasn't born here.

How does it happen? Someone comes from Hungary following 1956 and eventually becomes the head of MRC?

I was born in Györ. My father was a lawyer and he was also a lawyer for the Benedictine Order. So I went to school in Pannonhalma of the Benedictine Order. When I came out I was a second year chemistry student of Eötvös University. I decided that there was not much future to do science in Hungary after what had happened. My parents insisted that if I left, I should take my brother and sister with me. The three of us came out and I was in charge. We fixed up my brother in a school in Austria and my sister went to Belgium and I came to England by accident. It is a long story. My father had some connections in Vienna through the Benedictines. They put us up while we were deciding what to do. There were people at that stage in Vienna looking for students. Since Pannonhalma was an Italian-based school I was fluent in Italian and I was offered a scholarship in Padua but I wanted to go to an English-speaking country although I couldn't speak English. I wanted to do serious science and for that I had to learn English anyway. I bumped into a journalist who told me about two people in Vienna from Oxford University who were interviewing students. I went to see them and the next day I was on a plane to England. They didn't make a promise to be accepted by Oxford, it was typical, but four of us were taken to Oxford, where they started to interview us to see if we were suitable. A chemistry tutor at Merton College interviewed me, which is still my College. He couldn't speak anything other than English and I could speak several languages but not English. So he took out a Periodic Table and started to point and I had to show relationships and he convinced himself I knew enough chemistry to become a student in Oxford.

After completion of my doctorate, I went abroad for a year to Berkeley, California and worked with the Nobel-Prize-winner Melvin Calvin. Calvin shaped my science. This was the year after he won the Nobel Prize, the pressure was off, and he started to think what new things he could do. He decided to work on memory and he started some experiments. He was very imaginative. He taught me how to approach science and he said to me, "The first and most important thing is to choose the right problem. Having chosen the problem, you would have then to go after it and if you need to develop new methods you develop new methods." I also learned a lot from him about how to treat other people. He was tremendously good with his students, his postdocs; he was always on top

of everything in his seminar program. He would ask the most penetrating questions but without destroying the individual. He was not the typical aggressive American. The time I spent with him was my transition from chemistry to biochemistry.

When I returned to Oxford, I moved from Chemistry to the Department of Biochemistry where Hans Krebs was the head. He was convinced that the Oxford system where people had to teach tutorials and also lecture was totally against the scientific development of the individual. When I was in his department, I was offered a Fellowship and Tutorship at Merton College in organic chemistry although I was in the Biochemistry Department. I had to talk about this with Krebs because obviously this would affect my chances of getting a permanent position in Biochemistry. He said to me, "If you accept that job at Merton, I can guarantee that you will never

Hans Krebs (1900–1981, Nobel Prize in Physiology or Medicine for 1953) (courtesy of Edit Ernster).

At the opening of the MRC Clinical Magnetic Resonance Facility in 1983: Front row from left to right, Sir Anthony Epstein (of the Epstein-Barr virus fame), Dr. Peter Bore (a clinician in the MRC Unit), George Radda, the late Rodney Porter (Nobel Prize in Physiology or Medicine for 1972) and the late Sir David Phillips (courtesy of George Radda).

become a biochemist." He was so convinced that you couldn't link chemistry and biochemistry in such a way that you would be a productive biochemist. He also thought the teaching burden to be prohibitive. In spite of his strong opinion, I accepted the position at Merton and stayed in Biochemistry as my fellowship allowed me to stay there. Three years after I did get a job as Lecturer in Biochemistry.

Eventually, Krebs retired and Rodney Porter followed him. In 1980, I became a Fellow of the Royal Society. Krebs was no longer in the department but he was still alive and working hard somewhere else in the university. The very morning my election was announced he came over to the Department and for the first time ever he walked into my laboratory. Even when he was head he wouldn't come to my lab he was so reserved, he felt uncomfortable walking into individuals' labs. So this morning, 20 years after he had given me his advice, which I didn't take, he walked into my lab and said, "I thought you would never become a biochemist."

Your heroes?

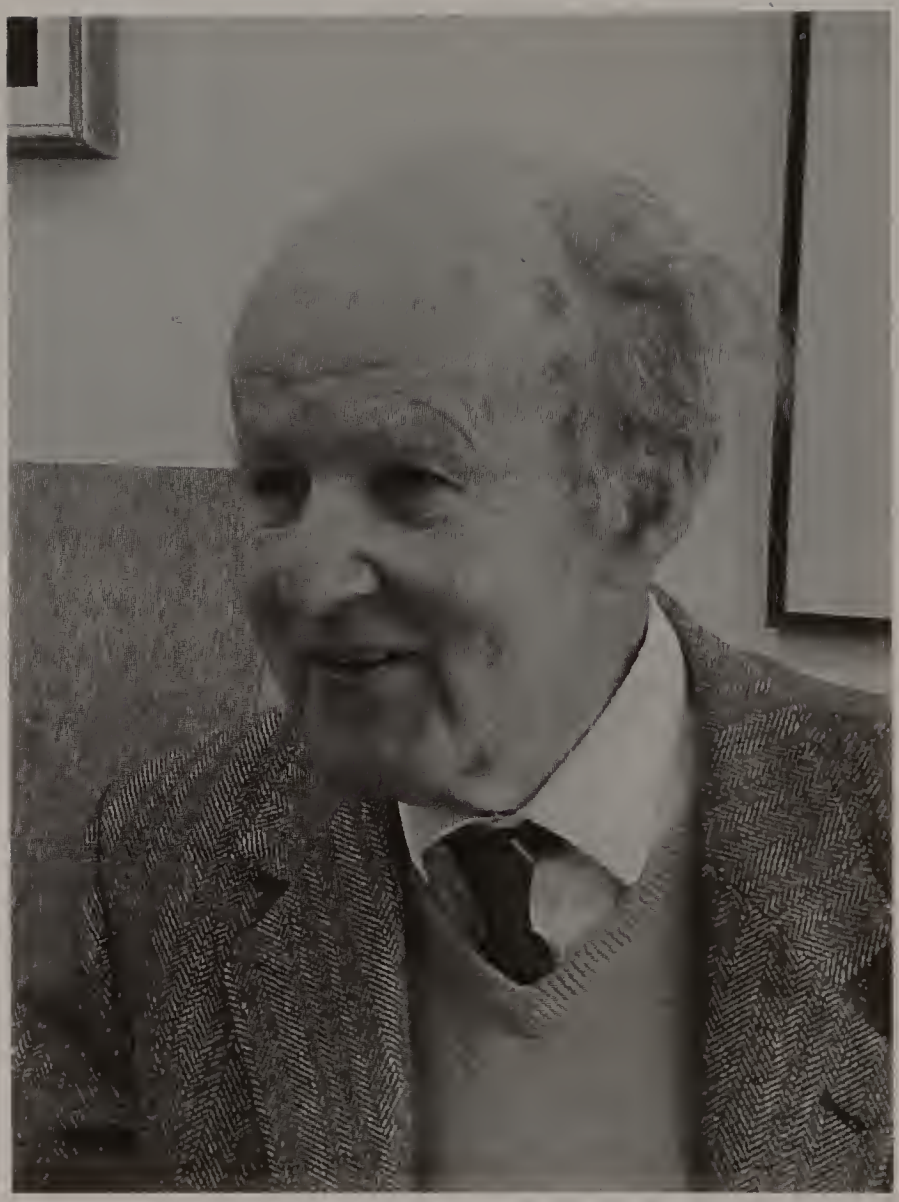
I look at Melvin Calvin as the one who had the biggest influence in the way that I think about science. Rodney Porter was another tremendous individual and he was very friendly and enormously supportive, very serious about his science, and had a very strong sense of humour. These two people probably had more influence on my life than anyone else did.

As of today, what would be your ambition?

To be able to play the piano like an artist. I play hopelessly bad. I wish I could sit down with a musical instrument and improvise and play beautifully.

Any message?

My message is an optimistic one about science and the biomedical field, that this is the century or the millennium of enormous changes of medicine based on science. I would like to encourage young people to think about this field of research.



Max F. Perutz, 2000 (photograph by Magdolna Hargittai).

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Max F. Perutz

Max Ferdinand Perutz (b. 1914 in Vienna, Austria) is a Member of the Scientific Staff of the Medical Research Council (MRC) Laboratory of Molecular Biology, Cambridge, U.K. He founded this laboratory and served as its first Chairman between 1962 and 1979. Dr. Perutz was co-recipient (with John C. Kendrew) of the Nobel Prize in Chemistry in 1962 "for their studies of the structures of globular proteins." Dr. Perutz is Fellow of the Royal Society (London), Foreign Associate of the National Academy of Sciences of the United States, Member of the Pontifical Academy, Foreign Member of the French Academy of Sciences, and member of many other learned societies. His many distinctions include the Royal Medal (1971) and the Copley Medal (1979) of the Royal Society. Since 1988, he has been in the Order of Merit of the U.K. whose membership is restricted to 24. We recorded our conversation in Dr. Perutz's office in the Laboratory of Molecular Biology in Cambridge on September 17, 1997.* It was then augmented in February 2000.

You came from Vienna to Cambridge in 1936 but have been back in Vienna since and you just returned from another visit yesterday. What emotions do you experience when visiting Vienna?

My first visit to Vienna was in 1949, very soon after the War. I had some dear friends in Vienna who had never become Nazis. I also had a cousin

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in Budapest who survived and moved to Vienna after the Communist takeover. The joy of seeing my friends and this family member was the overwhelming emotion I felt. I was very happy although I knew what had happened. The other thing was my nostalgia for the Austrian landscape, not for the people in Vienna, but for the landscape, which I adored. I went by train and it was a tremendous joy.

Have you had contacts with Austrian scientists?

I had a very nice professor of chemistry in Vienna, Fritz von Wessely. He was most encouraging and supportive to me. After the War, he wrote to me that he had a talented graduate student who would like to come to Cambridge for postdoctoral work. It was Hans Tuppy and Fred Sanger took him on in his laboratory. Later Tuppy became Professor of Biochemistry and Minister of Education in Vienna. I saw him last week in Vienna.

I was saddened to hear about the death of John Kendrew about two weeks ago. We had been planning a meeting for this week.

It was very sudden. He was brought to the hospital a Sunday night and died the next Friday night. I had no idea that he was ill, and learned only afterwards that he had prostate cancer. It suddenly erupted into metasteses and killed him very quickly.

Was he your student?

Yes, he was indeed. Our age difference was only three years. In 1945, he walked into my office, a young man in his smart wing commander's uniform. He asked if he could come and work with me as a research student. I was very flattered because I never had a research student, let alone one who had distinguished himself already in the War. But I was also embarrassed because I was working on this hemoglobin problem and I couldn't see any easy problem he could solve in three years and get a Ph.D. on it. At that time I was in the Physics Lab in the Cavendish, so I walked across to the Molteno Institute, the Biology Department, where I made my biochemical preparations and on the way I ran into the great respiratory physiologist, Joseph Barcroft, and mentioned my predicament to him. He was at that time very interested in the relation between adult and fetal metabolism and said, why don't you make a comparative study of adult and fetal sheep hemoglobin; I'll give you the blood. That's then what Kendrew did and that was his first paper.

M. F. Perutz, drawing by W. L. Bragg in 1964 (courtesy of the LMB Archives).

J. C. Kendrew, drawing by W. L. Bragg in 1964 (courtesy of the LMB Archives).

How long did you work together?

From 1945, for 20 years, until 1965. Really, Kendrew stopped scientific research when he won the Nobel Prize. Perhaps he realized that his talents were more in organization and diplomacy. He first joined the Committee of Defense, then various international committees. His appearances in the lab became rarer and rarer. He, of course, worked very hard to get the European Molecular Biology Laboratory approved by governments. This great laboratory in Heidelberg is his monument.

You are a member of the Order of Merit of the U.K. which has only 24 members. Coming from Vienna, isn't this rather extraordinary?

I'm not the only one. When I went to the Buckingham Palace to be received by the Queen and given the Order, I met Ernst Gombrich, the art historian, who was also receiving it. I'd never met him before and we discovered that we used to go to the same school in Vienna. After this we became great friends. He's a wonderful man who never opens his mouth without saying something interesting and witty. The friendship with Gombrich is the greatest benefit I got from the O.M.

Did your parents witness your success?

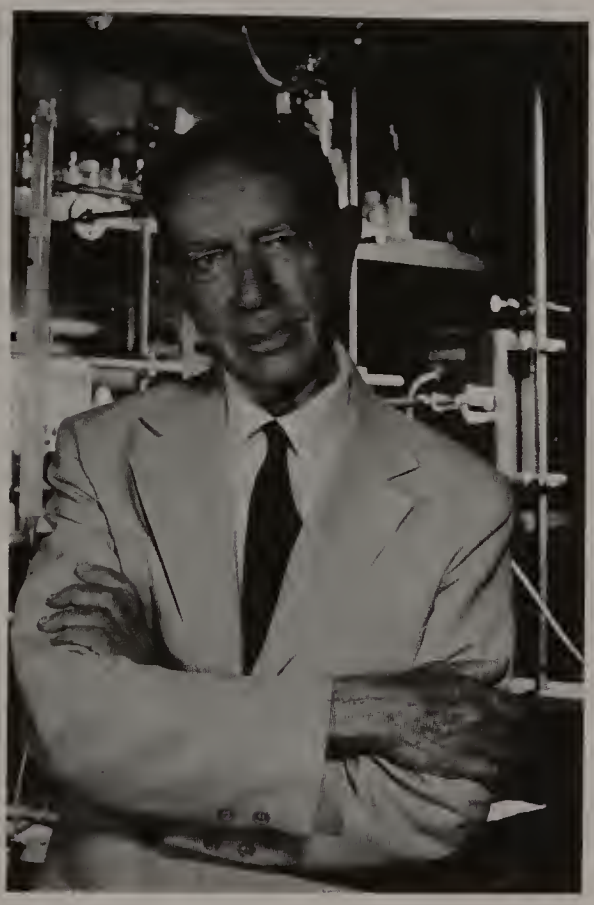
Only my mother. My father died four years before I was awarded the Nobel Prize and a year before the hemoglobin structure was solved. My mother was very sad about that. But she came to Stockholm with us and it was a tremendous treat for her.

Did your children follow you in any way?

My son is now Professor of Inorganic Chemistry at York University, but my daughter is an art historian and teaches history of art.

I read recently your description of your moving last meeting with Professor Felix Haurowitz.

I came to Cambridge in 1936, so it was before the *Anschluss*. Perhaps I should mention why I left Vienna. Professor Wessely gave a course on what we would now call bioorganic chemistry. He mentioned the pioneering work on enzymes and vitamins here in Cambridge at the Chemistry Department. That made me decide that I would like to do my Ph.D. in Cambridge. In 1935, I persuaded my father to let me do this. This wasn't such an unusual thing because



Felix Haurowitz (1896–1987) (courtesy of Max Perutz).

my elder brother had studied engineering at the ETH in Zurich. We were very internationally minded. In the Summer of 1937, I returned to Austria for my Summer holidays and went rock climbing as I usually did in the old days. It came to my mind that I didn't really have a subject for my Ph.D. yet. I remembered that my cousin Gina was married to a young professor of biochemistry in Prague. So I took the train to Prague, and went to see Haurowitz, Gina's husband. I suggested to Haurowitz that I make a structure analysis of hemin, the pigment of hemoglobin. But he thought it wasn't worthwhile because Hans Fischer in Munich had already synthesized it. He said why don't you try hemoglobin? He also told me of a man in Cambridge who might give me the crystals.

The next thing was that in 1938, Haurowitz did a very important experiment which showed that hemoglobin changes its structure every time it takes up and releases oxygen. Hemoglobin with and without oxygen crystallizes in different forms. They were different phases. He published this in Hoppe-Seyler's *Zeitschrift für physiologische Chemie* [**1938**, *254*, 266] as a short note which, at that time, few people would have noticed, and

I wouldn't have noticed but for the fact that he was my cousin's husband and sent me a reprint of it. That was a crucial step in my career.

When the Germans annexed Czechoslovakia, Haurowitz first emigrated to Istanbul and had a chair of biochemistry there during the War. However, he realized there was no career there for his children, so he emigrated again and became Professor of Biochemistry in Bloomington, Indiana, where he stayed for the rest of his life. I used to visit him there whenever I was in the neighborhood. I visited him again when he was already over 90.

This's when he told you about the difficulties of publishing his paper in Leipzig and the Editor's ordeal for having published this paper by a Jewish scientist.

Yes. But there is an appendix to the story I had published. There is a Professor of Genetics in Cologne, Benno Müller-Hill, who has written a book, *Tötliche Wissenschaft*. He wrote about the terrible criminal activities of German scientists during the War. Müller-Hill checked on the story of Haurowitz and he said Haurowitz must have imagined it; nobody would have cared at that time that Hoppe-Seyler's *Zeitschrift* published a paper by a Jew in Prague and the Editor never got into trouble for it.

There's quite a gallery of pictures on your wall. I see J. Desmond Bernal's photo among them. You have been quite critical of him.

Originally I came to study with him in Cambridge and was with him for two years. Then he became Professor of Physics at Birkbeck College in London. But I was enrolled as a research student in Cambridge, so I stayed here. Bragg succeeded Rutherford as Cavendish Professor and, of course, Bragg was the inventor of X-ray analysis. When I showed him my X-ray pictures of hemoglobin, he was fascinated by the idea of extending X-ray analysis to the molecules of the living cell. I really owe my scientific career to his support.

*Would you care to say something about the Bragg-Kendrew-Perutz paper, "Polypeptide Chain Configuration in Crystalline Proteins" [*Proc. Roy. Soc. **1950,** 203A, *321–357] Recently* The Chemical Intelligencer *[***1996,** 2(1), *32–38] published Linus Pauling's heretofore unpublished story of the discovery of the alpha-helix. There he describes the importance of his gas-phase electron diffraction studies of the structure of small molecules and the resonance theory in helping him realize that the peptide bond configuration should be planar.*

The awful thing is that Kendrew and I didn't know that the peptide bond was planar. Perhaps the most important observation that misled us was the X-ray pictures of alpha-keratin by Astbury at Leeds. Astbury discovered that protein fibers gave two kinds of pictures. Wool gave a picture with 5.1-Å meridional reflection, but when he stretched wool in steam, that disappeared and a reflection at 3.4 Å appeared instead. Astbury argued rightly that the stretched wool corresponds to an extended polypeptide chain and the 5.1 Å to a folded one. So Kendrew and I thought we must build molecular models with a repeat of 5.1 Å, and we built a variety of helical structures and nonhelical structures, all with that repeat. We noticed that we had to strain our models rather to get that repeat but we didn't see any way out. And we didn't realize that we had to keep the peptide bond planar. If we had, our model would have been even more strained. We would have had to force it even more to achieve the 5.1-Å repeat. Pauling, on the other hand, disregarded Astbury's pictures; he built a model that was stereochemically reasonable. He kept the peptide bonds planar and made the best possible hydrogen bonds.

One Saturday morning I went to the Cavendish Library and found this series of papers by Pauling and saw his structure and it looked stereochemically right and yet it didn't seem right because it didn't have the right repeat. My mind was in turmoil and I kicked myself for having missed this. I cycled home to lunch and my family wondered why I didn't listen to anything they said. Suddenly a thought occurred to me. If there was really the regular axial repeat of 1.5-Å of the residues along the Pauling model which he indicated, there must be a reflection at 1.5 Å on the meridian which has not been reported. I remembered that I had a horse hair in the drawer in the laboratory so I cycled back to the lab.

There was also another thing. I had visited Astbury's lab and seen his setup. He had a goniometer head and behind it the photographic film which was quite narrow. If there were a 1.5-Å reflection, the Bragg angle would be 31° and the reflection would occur at an angle of 62° from the incident beam. I realized that Astbury's plate would have missed that. Moreover, Astbury always had the fiber axis at right angles to the X-ray beam and I realized that to get that reflection, one would have to incline the fiber at 31° to the incident beam to fulfill Bragg's law.

So I went back to the lab, found my horse hair, set it up at an angle of 31° to the beam, and put a cylindrical film around it, so that it would catch reflections at high angles; I exposed it for 2 hours, and developed the film with my heart in my mouth. And to my surprise, what I found

was a strong reflection at 1.5 Å which, I realized, excluded all models except the Pauling-Corey alpha-helix.

What next? That was on a Saturday. On Monday morning I rushed into Bragg's office and told him what I'd discovered. Bragg asked, how did you think of that? I told him it was because I was so angry that I hadn't thought of that structure myself. To which Bragg replied coldly, I wish I'd made you angry earlier.

You did your experiment on Saturday and you rushed into Bragg's office on Monday. How could you wait so long? Why didn't you let him know during the weekend?

Relations were a little more formal then than now. I wouldn't have disturbed him on Sunday at home.

How much modeling went into the hemoglobin study?

None. None at all. It was a question of solving the phase problem. I should perhaps say, though, that I did make an earlier model where I proposed what turned out to be alpha-helices strung out in parallel, and this turned out to be a complete nonsense. To solve the structure I had to solve the phase problem, which was generally regarded as insoluble for such a large structure.

In 1953, I discovered that it could be solved by the method of isomorphous replacement. I compared the X-ray diffraction pattern from a crystal of pure hemoglobin to one from hemoglobin to which I attached two mercury atoms. In 1936, J.M. Robertson in Glasgow had solved the structure of an organic dye with this method, but that dye contained 58 atoms while hemoglobin contains 10,000. Everybody believed that attaching a heavy atom to the protein wouldn't have any measurable effect on the diffraction pattern. I had measured, for some other purpose, the absolute intensity of reflections from the hemoglobin crystal, that is, the fraction of the incident beam that is diffracted. That told me that the scattering contributions of most of the light atoms, which are spread over a large volume, cancel by interference, while in a heavy atom the electrons would be concentrated at a point and they would all scatter in phase. Therefore the heavy atom would make a measurable difference to the scattering and that was borne out by the first experiment I did. So I found that the phase problem could be solved by the heavy atom method. That was my

Max Perutz preparing for a BBC broadcast around the time of his Nobel Prize in 1962 (courtesy of the LMB Archives).

life's most important discovery, because it opened the whole field of protein structure to X-ray analysis.

When you were awarded the Nobel Prize, the hemoglobin structure was not yet completed.

No, we had only a low-resolution model at 5.5-Å resolution. But it showed a lot. It showed that the fold of the chain in hemoglobin was the same as in Kendrew's myoglobin. That was vital to give people confidence of the result, because no conceivable error could have led to the same structure emerging in two independent X-ray analyses based on pure physics without any assumptions about the chemical structures we were trying to solve.

It has proved then very lucky for you also that Kendrew had joined you.

Yes, indeed. It was marvelous that these structures turned out to be so closely similar.

You didn't stop working after the Nobel Prize.

No. I am still working.

Have you also done public service?

Very little. I helped to found the European Molecular Biology Organization (EMBO), of which I was the first Chairman for six years. Apart from that I have always avoided committees.

If today somebody would come from Vienna or Prague,

or Budapest,

what would be your advice for him or her, or for other young people, for that matter, about starting a research career?

There was a very wise man in Paris, French but of Polish origin, André Lwoff, who said, the most important thing for any young scientist to do is to find himself a good "patron" in French, a good supervisor or mentor, "Doktorvater" in German. That would be my advice.

Lise Meitner's picture is in your wall gallery. In the July 1997 issue of The Chemical Intelligencer, *there is an article about The Wall of*

Fame in the Chemistry Department of the Technion. They have collected famous chemists' signatures. Your signature is there. The only criterion was that the person had to be a great scientist. When Lise Meitner was asked, she refused to send her signature there, saying that she was not Jewish although it was clearly stated that this Wall of Fame had nothing to do with it. She appeared to be over-careful in dissociating herself from anything Jewish.

Let me quote for you from an article I wrote about her [*The New York Review*, February 20, 1997]. When the Hiroshima news came out she was "[S]hocked beyond words, she walked alone for many hours. Her friends had never seen her so distraught. Worse, reporters pursued her since she had suddenly become a public figure who shared responsibility for the atomic bomb. Under a headline FLEEING JEWESS, one news story described how she escaped from Germany with the secret of the bomb and handed it to the Allies.

In September 1945, Meitner wrote to her sister:

"I feel like an impostor when American Jews ... praise me especially because I am of Jewish descent. I am not Jewish by belief, know nothing of the history of Judaism and do not feel closer to Jews than to other people. And just now, when one wishes so strongly that all racial prejudices be eliminated from the world, isn't it unfortunate if Jews themselves document such racial prejudice?"

There were some periods in history when people thought they could forget about their being Jewish.

So did my parents.

But then others came to remind those who forgot.

That is true. But I am always very disturbed by Jewish chauvinism that the Jewish response to anti-Semitism is to be as intolerant as their enemies. In London this creates more anti-Semitism, but here there is hardly any. The wonderful thing about British academic life is that there is no anti-Semitism at all.

I am of Jewish descent, but don't feel any closer to Jewish people than to anyone else. I always like to judge people by what they are, by their character, personality, abilities, but I am not very interested in whether they are Jews or Indians or Americans. Of course, my children are aware

of their origin, they are indeed. We never kept it secret from them. It happens that parents keep it from their children, and it is very sad when it does. Before we started recording we talked about our heroes. One of my heroes was a biologist, Professor David Keilin. He was born in Moscow, educated in Warsaw, studied in Paris, came here in 1915, and made one of the great discoveries of biochemistry. I loved him very much. After his death his daughter became very angry with her parents because they had kept their Jewish origin from her. To me it was always obvious that Keilin and his wife were Jewish.

> At the beginning of 2000, I had an opportunity to ask Dr. Perutz about his recent interest. My wife and I were spending three months at the Laboratory of Molecular Biology and could observe how busy he was, yet always friendly and readily available. Here is what he told me on February 7 about his work:

I work on the Huntington disease problem. As you are interested in history, it is amusing how I got into this. I have always been very interested in the regulation of the oxygen affinity of the heme by the globin. It struck me that the dissociation constant of oxygen can vary over a range of 10^5, an enormous range. There was a hemoglobin discovered by David Keilin in 1925 in a parasitic worm, *Ascaris*, which has an enormously high oxygen affinity. I always wondered why. That was a difficult problem, because the hemoglobin is an octamer of molecular weight 368 kilodalton or so, not something that you can easily determine the structure of. Then, eventually I found a group in Antwerp, interested in invertebrate hemoglobins. There was a graduate student there, I. de Baer and he determined the amino acid sequence of *Ascaris* hemoglobin. That shows an unusual feature. The C-terminal amino acid sequence, glutamic acid, glutamic acid, lysine, lysine, glutamic acid, glutamic acid, histidine, histidine, and so on, repeated four times. I had never seen anything like this. Then I realized that it must be a polar zipper, which holds the octamer together. I thought that this might not be the only one in nature and asked a colleague here to search the database and he found some others. He also called my attention to long repeats of glutamines in some *Drosophila* proteins, some transcription factors. I was intrigued by that and built a little atomic model. I found if you have a string of glutamines, two beta-strands would join forming hydrogen bonds between the amide groups of both the main chain and

the side chains. I wrote a little paper on polar zippers and included this model, held together not by charged groups but by dipoles. While that paper was in press, I came home from a lecture in Leicester one night and read the *New Scientist* and found an article about the discovery of the gene for Huntington disease. This gene codes a very large protein of over 3000 amino acids, but the only difference between the normal protein and the protein of people afflicted by this terrible disease consists of the length of a glutamine repeat. The repeat varies in length in normal people but it is never longer than 37 glutamines, but in people with the disease it is longer, above 40, and can be as high as over 100. The longer the repeat, the earlier the disease sets in and the more severe it is. I was very struck by this and thought that the polar zipper action of the glutamines might provide the clue to the molecular mechanism of the disease. I asked a chemist here in the Lab to prepare some synthetic polyglutamine and to make it soluble. This gave a circular dichroism spectrum characteristic of pleated beta-sheets. I wrote a little paper in which I proposed that the elongation of the glutamine repeats made the protein aggregate in neurons. These aggregates might actually kill these neurons. I published this paper in 1994. For the next three years there was no evidence of such aggregates. Then, two people in London, Gillian Bates at Guy's Hospital, a geneticist, and Stephen Davies at University College who is a lecturer in anatomy, discovered the aggregates in mice that were made transgenic for a fragment

Max Perutz lecturing (photograph by Alan R. Fersht, courtesy of Max Perutz).

of this protein, containing the glutamine repeats. They found that with repeats of 18 glutamines the mice were healthy and with 120 glutamines they developed the symptoms of the disease. Stephen Davies discovered aggregates of this protein in the nuclei of neurons in the brain, in the striatum and in the cordex. After this, people in the States looked at the post-mortem sections of patients again, and found these aggregates there where they had been overlooked before. We are now in the position that seven other neurodegenerative diseases have been found to be due to extension of glutamine repeats and nearly all of them have aggregates in the nuclei of the affected neurons. There is still a lot of skepticism whether this can really be the cause, but in fact no one else has proposed any alternative mechanism. It really looks that this is right. What could I do? My first step was to incorporate a glutamine repeat in a small protein of known structure. I thought that might provide a clue. A graduate student Kelvin Stott did that. The outcome of this work was quite different and unexpected. Adding an extra loop of glutamine repeats actually made these proteins form oligomers, in a process known in the protein business as domain swapping. It is not out of the question that something like that actually happens in the disease, but so far there is no evidence that it does. What I was trying to do was to investigate the structure of these proteins. The Huntington protein has 3140 amino acid residues, and there is no hope of crystallizing it and getting its structure. But there is another protein, which is the cause of Macado-Joseph's disease, which has only 360 amino acid residues. I thought it should be possible to crystallize this. I cannot have a large research team here. I have one postdoc working with me, but luckily I found a group interested in the problem in Milan. They are cloning this protein, making it with various lengths of repeat. They also purified it and sent it here and Wu Chen is trying to crystallize it. He has been trying for a long time and until recently nothing has crystallized. But last Friday, three days ago, he showed me some of his preparations. Looking down his microscope, I actually found that one of his preps contained microscopic needles. I was very thrilled. Although they are much too small for X-ray analysis, this is the first time that we have actually found a prep that can be crystallized and I am sure that we will succeed.

Last year I visited Seymour Benzer ...

He stimulated others to make *Drosophila* with Huntington disease or related diseases. Nancy Bonini at UPenn made *Drosophila* transgenic for one of

the glutamine diseases. She found indeed degeneration of the affected cells, and she got deposits of the protein in the cell nuclei. This may be very useful because *Drosophila* would be an ideal organism for trying possible drugs against the disease.

Returning to structural aspects ...

For a long time the dogma was that you cannot see hydrogen atoms by X-rays. Then Cochran built a rather primitive counter spectrometer here in the Cavendish and measured intensities aligning very accurately. He showed that you can actually see hydrogens. I am saying this because recently I have come across a protein paper, where, thanks to modern techniques of cryo-crystallography, high resolution was achieved and we can now see hydrogen atoms even in a protein molecule. Precision organic chemistry and protein crystallography is merging.

One other interesting instance was in the 1980s when an American colleague of mine, Bob Abraham and I were working on drug binding to hemoglobins. There was one drug, an antilipid dimic agent, which bound to human dioxy-hemoglobin. There we noticed a phenyl ring of the drug, which was juxtaposed to an imino group of the protein. The N–H pointed to the π-electrons of the phenyl ring, pointing straight to the center of the ring. It struck me as a hydrogen bond with the π-electrons of the benzene ring acting as the electron donor. In this case it was protein structure, which led to the discovery of this kind of hydrogen bond, which has been seen now as a frequent structural feature. Last week I came across a paper in *Acta Crystallographica* of a neutron diffraction study of an organic compound demonstrating such an interaction. The energy of the hydrogen bond was calculated to be 16 kJ/mol.

Richard Henderson, 1998 (photograph by I. Hargittai).

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Richard Henderson

Richard Henderson (b. 1945, in Edinburgh, Scotland) is the Director of the Laboratory of Molecular Biology of the Medical Research Council of the United Kingdom (MRC LMB). He got his B.Sc. in physics from the University of Edinburgh and has been with the MRC LMB since 1966, first as a Ph.D. student of Cambridge University and later as a staff member. Between 1970 and 1973, he was a postdoctoral fellow at Yale University. He was elected Fellow of the Royal Society in 1983 and Foreign Associate of the U.S. National Academy of Sciences in 1998. He has been awarded several prizes including the 1993 award of the Louis Jeantet Foundation in Geneva and the Aminoff Prize (Sweden) jointly with Nigel Unwin in 1999.

The first Director of LMB was Max Perutz followed by Sydney Brenner, Aaron Klug and then Richard Henderson in 1996. Richard Henderson's administrative duties have not diminished his enthusiasm for research activities, and I asked him about them at the beginning of our conversation on October 8, 1998. The second part of the conversation was about the LMB.*

Currently, I work on the structure of proteins in cell membranes. I have been interested in this for 25 years. Before that, I was an X-ray protein crystallographer working on enzyme structure. Membrane protein structure is still a difficult area. Originally, I picked what I thought were the most

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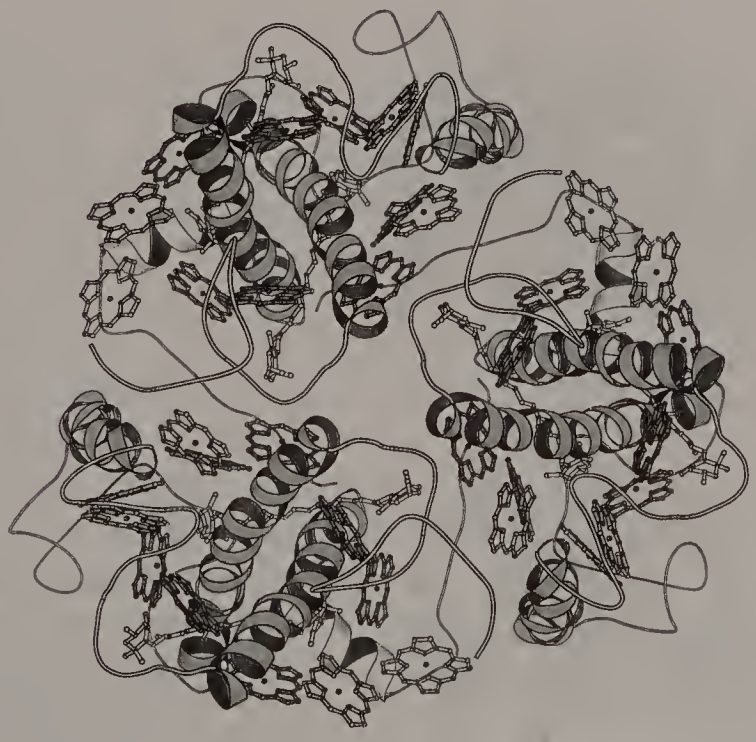
Bacteriorhodopsin, the light-driven proton pump from halobacteria. The retinal chromophore is shown in the center of the seven α-helices. Picture made using coordinates from Grigorieff, Ceska, Downing, Baldwin, and Henderson, *J. Mol. Biol.* **1996**, *259*, 393–421 (courtesy of Richard Henderson).

interesting structures, the voltage dependent ion channels, which underlie all human physiology and are important in medicine and pharmacology. However, after about three years working on these ion channels as a postdoc, I realized that it might be better to take up some simpler membrane proteins of which I could get grams. Thus, since 1973, I have worked almost continuously on bacteriorhodopsin, which is a light-driven proton pump from bacteria discovered by Walther Stoeckenius around 1968. We have broadened our work to other membrane proteins such as the seven-helix G-protein-coupled receptors. Many of these membrane protein structures are potential targets for development of future drugs and pharmaceutical products, for example, the neurotransmitter receptors and transporters.

Over the years, Nigel Unwin, also of LMB, and I have built up a mutual interest in the field and we have come to an understanding that he works on ion channels and I work on seven-helix receptors and pumps.

I have mentioned our scientific goal, but how to get there is another matter. I, like many others, began by trying to make three-dimensional protein crystals of the membrane proteins, and we could not get very good crystals. Then, some years ago, Nigel, who is a very good expert in electron microscopy, myself, and others began to collaborate to develop electron microscopy into what it is today, a method of atomic-resolution structure determination for two-dimensional protein crystals which are one molecule thick. Bacteriorhodopsin forms such a system *in vivo* — it was a natural

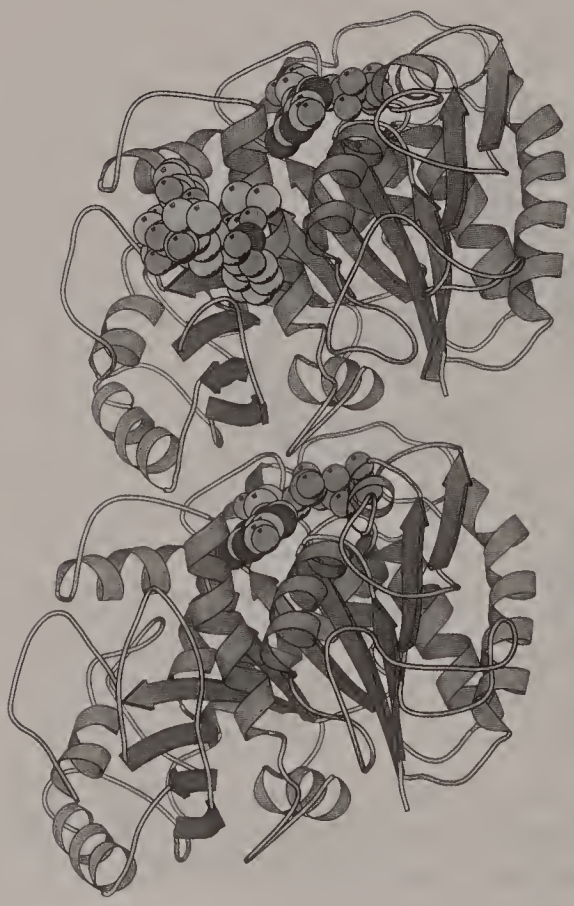
Nigel Unwin and Richard Henderson between Ernst Ruska and Mrs. Ruska at a scientific meeting. Ruska (1906–1988) designed the first electron microscope in the 1930s and was awarded the Nobel Prize in Physics for it in 1986 (courtesy of Richard Henderson).



Light-harvesting complex from green plants. Each of the three protein molecules in the trimer has 12 chlorophylls and 2 carotenoids bound. Picture made by Dr. Werner Kühlbrandt based on coordinates from Kühlbrandt, Wang, and Fujiyoshi, *Nature* **1994**, *367*, 614–621 (courtesy of Richard Henderson).

two-dimensional crystal. Since then, many membrane proteins and other proteins have been studied as thin crystals, and there are now three atomic-resolution structures determined using electron microscopy. One was done here, the bacteriorhodopsin structure, and the other two by a former student of ours, Werner Kühlbrandt, who is now a scientific member of the Max Planck Society, and by a former co-worker of ours from Lawrence Berkeley Laboratory, Ken Downing. The atomic-resolution structures they have determined by electron microscopy are the light-harvesting complex from green plants (Kühlbrandt) and the $\alpha\beta$-tubulin complex (Downing). The three structures are shown in the figures, and the original references are given in the figure captions.

The main advantage of electron crystallography over X-ray crystallography is in the 10^4–10^5 times greater cross section for scattering, allowing us to use much smaller crystals. They can be one molecule thick, and their diameter need not be larger than half a micron. That would be about 5000 molecules in each crystal. With X-rays, you need 10^{10}–10^{12} molecules in each crystal. Even back in the early days, about 25 years ago, Nigel and I realized



The $\alpha\beta$-tubulin dimer. The α-tubulin is at the bottom and β-tubulin at the top. Each $\alpha\beta$-tubulin dimer has one taxol molecule bound, and each monomer has a GDP or GTP nucleotide bound. Picture made by Dr. Ken Downing based on coordinates from Nogales, Wolf, and Downing, *Nature*, **1998**, *391*, 199–203 (courtesy of Richard Henderson).

that electron crystallography had the advantage that it did not need the heavy-atom derivatives that are required to determine phases in protein crystallography using X-ray diffraction. Instead, the phases of the Fourier components are determined directly from the electron micrographs — this was realized first in the work of Aaron Klug and David DeRosier at LMB in 1967. They worked on negatively stained specimens. The next important step in biological electron microscopy was the introduction of the freezing technique in the sample preparation, around 1982 by Jacques Dubochet, then at the European Molecular Biology Laboratory (EMBL) and now in Geneva. Dubochet and his colleagues at EMBL invented the technique of plunge-freezing a thin (500 Å thick) film of water on an electron microscope grid into liquid ethane cooled to near liquid-nitrogen temperature. This allowed the specimen of protein or virus particles to be suspended in a thin film of amorphous, vitreous ice which could be transferred into the electron microscope vacuum and imaged, giving pictures of unstained molecules embedded in a medium very similar to their normal aqueous environment. Utilizing the modern computers, today we can do almost anything by electron microscopy that X-ray crystallography can do.

There is still one area that has to be developed and on which we are working at the moment. This is the problem of determining the structure of some important membrane proteins, which are rather unstable. Some of them last less than a day or two in detergent at 4°C, and they would be gone in a few minutes at room temperature. The knowledge of their structure would be very important, but I am rather pessimistic about whether we will ever be able to determine their structure by crystallization. Our current thought is that we should further develop electron microscopy so that we no longer need entire crystals, but would need only single particles. There are virus structures and big complexes that have been studied at medium resolution, but not yet at atomic resolution, by electron microscopy. The idea is to push electron microscopy so that we can work with single particles at atomic resolution and then by some tricks make the membrane proteins form sufficiently big particles.

I have shown theoretically that, in principle, the size of single particles that can be studied at atomic resolution is limited only by radiation damage, and it is possible to determine the structure of any molecule, without crystals, provided we can collect 10,000 images of it. This is the theoretical number. We cannot make do with one single molecule, that is, we cannot have single-molecular electron microscopy, we need to have 10,000, and in practice probably more than that. All other difficulties can be overcome but not

the radiation damage. Thus, we need 10,000 molecules and they need be large enough so that their image contains the information needed to determine the position and orientation of the particles. If the molecules are too small to determine their orientation from images of individual proteins, we need to make them join together so that they produce large enough particles, which are also atomically ordered. For the ribosome, for example, two groups now have 12-Å resolution by electron microscopy. The best X-ray crystals of ribosomal subunits show 3-Å resolution, so we know these structures can be atomically ordered, but there are many other systems where no X-ray information is available.

To summarize, our goal is to develop electron microscopy into such a technique of membrane protein structure determination that it can be employed in a systematic and reliable way. The present situation, where crystallization is a creative art, can then be replaced by something more systematic and analytical. Once we have that, the pharmaceutical companies will have faith in our methods, and these activities will then become company work rather than the present government-funded long-term research. This is not a too distant goal; it may be possible to achieve this in a few years' time.

At LMB there are more Nobel laureates working today than in even some of the most industrialized nations. How intimidating is it for you to be director of such an organization?

It is a delight. Let me tell you the story of how I decided to come here in the first place. When I was a young student in Edinburgh, doing physics, I looked around in Britain at what was going on in biophysics. I found Maurice Wilkins at King's College in London, David Phillips at Oxford, Jack Dainty in Norwich, and R. D. Preston at Leeds. I wrote around and decided in the end that I would go to King's. After I had made my decision, I went to see my professor in Edinburgh, William Cochran, who had been in Cambridge (he was one of the authors of the famous Cochran/Crick/Vand paper on helical diffraction theory [*Acta Crystallogr.* **1952**, *5*, 581–586]. Cochran said, "I do not think you should go to King's College in London. You should write to my friend Perutz." So I wrote to Perutz in Cambridge and visited his lab on a Saturday morning in February after I had visited King's on a Wednesday several months earlier. In Perutz's lab there was far more work going on on a Saturday than there was at King's on a Wednesday. So I backed out, changed my plans, and have

Richard Henderson with Max Perutz, the founder of the LMB, 2000 (photograph by I. Hargittai).

Some of the LMB Nobel laureates: James Watson, Max Perutz, César Milstein, Frederick Sanger, John Kendrew, and Aaron Klug (courtesy of the LMB Archives).

been here ever since. Once you work in this environment, you do not have any desire to go for anything less.

My role is now to keep LMB as exciting as it has been and maintain what is a great tradition. An important part of this is keeping in touch with the previous people rather than feeling intimidated by them. To our delight, the Nobel Foundation keeps finding work at LMB that they favour. [1958, Fred Sanger; 1962 Max Perutz and John Kendrew, Francis Crick and Jim Watson; 1980, Fred Sanger; 1982, Aaron Klug; 1984, César Milstein and Georges Köhler; 1997, John Walker.]

The Lab used to be much smaller, but now about 400 people work here. There are four divisions, and the division heads decide jointly on questions of tenure with advice from outside experts and junior members of the Lab. A committee of more junior members does the original recruiting. We have a kind of federal system in which everybody has some influence and some ownership of the Lab as a place to work. It is not a communist system, but there are other ways to distribute the power. We do not have much grant proposal writing to do, we have no teaching to do, and a minimal amount of administration. I spend most of my time talking to people. Occasionally I have to write a letter. Every five years we have to do a report and submit our plans to MRC and that is time-consuming. It is strongly reviewed and the results can reduce or increase our funding. So far, we have had a steady increase of our funding from MRC, and members of the Scientific Staff of LMB value its status as an MRC Laboratory.

I have heard Robert May,[1] *the chief science adviser of the British government, stressing the importance of the benefits of fundamental research in the U.K.*

Our primary role is doing new research in new areas, and this research should eventually benefit the country and the world. The primary role is not to make money, nor to transfer technology. Alongside that, however, whenever anything is discovered that has the possibility of application, it is patented and marketed either by us or by the technology transfer group of MRC. There are many patents every year, and the scientists are encouraged, if they are interested, to be available part of the time to act as consultants or to start up their own companies. People get paid much more as consultants than in the Lab, and it is fine as long as it does not take away more

[1]Robert May was elected President of the Royal Society (London) in 2000.

than 15 percent of their time. Quite a lot of people, about a dozen of the 50 or so tenured scientists, are engaged in such activities. Some of our technicians also act as consultants. Over the years, many people have started companies from the Lab. The first such company, called Celltech, was organized for the production of monoclonal antibodies. Its founders first took a leave of absence from the Lab but eventually stayed with the company. MRC gets a portion of the company income and so does the Lab, and there is ample financial incentive for the participating scientists. The commercial income for the Lab though is still only a very small portion of our annual budget of about £15 million, the major part of which comes from MRC. But this income contribution from licenses and royalties has steadily increased over the years.

Aaron Klug, 1998 (photograph by I. Hargittai).

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Aaron Klug

Aaron Klug (b. 1926 in Lithuania) is a Member of the Scientific Staff of the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB), Cambridge, U.K. He was President of the Royal Society (London), 1996–2000. Dr. Klug was the recipient of the Nobel Prize in Chemistry in 1982 "for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid–protein complexes." He grew up in South Africa, having been brought there by his parents as a child of 2. He received his B.Sc. from the University of Witwatersrand, Johannesburg, in 1945, his M.Sc. from the University of Cape Town, in 1946, and his Ph.D. from the University of Cambridge in 1952. He worked at Birkbeck College, University of London, between 1954 and 1961 and has been with MRC LMB since 1962. He served as Director of LMB from 1986 to 1996. He was a teaching Fellow of Peterhouse (College) and Director of Studies in Natural Sciences from 1962 to 1986 and is now an Honorary Fellow.

Dr. Klug was elected Fellow of the Royal Society in 1969, and his many distinctions include the Copley Medal of the Royal Society (1985). He is a member of the Order of Merit of the U.K., whose membership is restricted to 24.

The interview took place in Dr. Klug's office in the Laboratory of Molecular Biology on October 9, 1998, and the text was finalized at several sessions in February and March 2000.*

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*This interview was originally published in *The Chemical Intelligencer* 2000, *6*(4), 4–13
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At the conclusion of your Nobel lecture in 1982, you predicted that the subjects of research in molecular biology would become increasingly complex and made a specific point about structural studies connecting the cellular and the molecular.

It is happening in the way that people have been using electron microscopy, for example. There are now low-resolution structures for the ribosome, the biological factory, which makes proteins. There is also now an X-ray structure to about 8-Å resolution at Yale on the 50S subunit of the ribosome. This has a million kilodalton molecular weight. Another group is analyzing crystals of the 30S subunit, the second "half" of the ribosome. John Walker's enzyme F1 ATPase had a mass of 330 kilodaltons, which was a triumph for crystallography at the time.

One of the things we had to do when studying the nucleosome was to show that it was biologically relevant. Our critics at that time thought that what we were studying was artificial. But, in fact, we did a lot of studies by X-ray diffraction on intact nuclei and we also used enzymatic digestion as a probe to cut the DNA inside the nucleus, comparing it with the isolated nucleosome. More generally, we used all sorts of methods to make sure that the components we studied *in vitro* represented not artifacts of reconstruction but the real thing.

You obviously convinced your critics.

Yes, but this was unglamorous work. It is the biochemical background, not often stressed in the papers, which, in the main, show only the results. Our critics could not believe that something so highly ordered as a nucleosome could be formed inside the cell, but we were able to crystallize the nucleosome. We now know that there is considerable order in the cell. Of course, it is not perfect crystalline order, but it is ordered. It is important that we carry out biochemical and biological tests along with the crystallographic studies. People call me a crystallographer and I do do crystallography, but it is biochemical crystallography, that is what we should call it. The chemistry is vital.

In your research, structure determination and new methodologies appear to have equal importance.

Absolutely. Without the new methodology, we would not have been able to solve the structures. When we started out to use electron microscopy

for our virus structure studies (to complement the X-ray work), we thought that we would just get an overall view of the structure. People had not realized that you could extract much more information from electron microscope images. In 1969, when we demonstrated the first three-dimensional image reconstruction of virus particles and bacterial flagella at a meeting in New York, Sturkey, an electron diffractionist, called it a "load of crap." What he did not understand was that we were dealing with relatively weakly scattering objects. We had demonstrated this, for example, on multilayers of cell walls, which could be analyzed by electron microscopy and diffraction, taking into account the overlapping layers. A tremendous amount of background work went into three-dimensional image reconstruction before we began to understand what was going on. Sturkey had a theoretical point that we were ignoring multiple scattering, but we justified it. Because of your own research in electron diffraction, you will understand the point about multiple scattering and so do I and so did Sturkey. I have a Ph.D. in Physics and do know some physics and mathematics.

When you say "methodology," I started out with electron microscopy with the simple view that it was well understood. In fact, I realized soon enough that this was not the case. I had the good fortune to be a non-expert. When you are a non-expert, you do not come with many presuppositions. There were various people working in the field trying to get "the perfect picture," and I realized that there was no such thing. I introduced the approach of taking a series of micrographs in the electron microscope at various degrees of defocusing and then correcting them for the contrast transfer function. With this method, we could create an image of transparent objects, that is, nonstained biological specimens.

The technology developed in the course of practical studies. We started out with a real problem in a helical virus, and I soon realized that we could make a three-dimensional reconstruction by using the theory of helical diffraction. Every time you tilted the specimen, you could recover another function in the mathematical expansion of the electron density. I had developed the approach for Rosalind Franklin's X-ray studies of the tobacco mosaic virus (TMV). Later, I saw that it was a special case of a more general principle in Fourier theory.

The method also became the basis of the principle of the X-ray CAT scanner. Hounsfield and Cormack received the Nobel Prize in 1979 for computer-assisted tomography (CAT). Hounsfield read my *Nature* paper of January 1968 and took out a patent for CAT in August 1968. I had realized earlier that you could apply it to medical radiography, and I went

Aaron Klug with the tobacco mosaic virus model at the LMB in Cambridge, England, 2000 (photograph by I. Hargittai).

to see some radiographers, but they told me that they did not need this "fancy stuff." They said, "We understand exactly what we see in a medical X-radiograph," but I asked them about the radiation doses used.

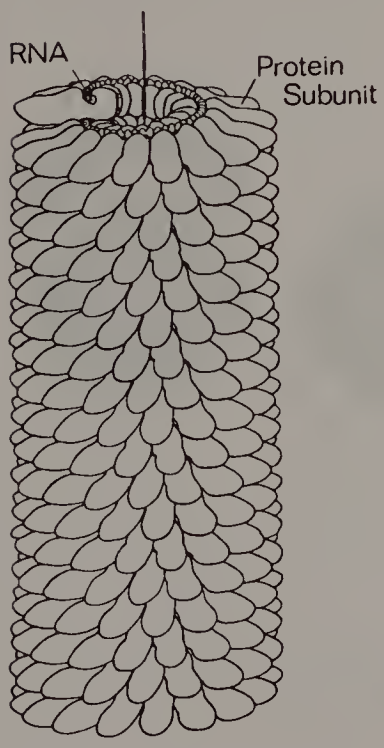
The X-ray tomography of the time used a moving source of X-rays and a moving film, so all the density, except in one purely geometrical optics plane, was out of focus, the rest blurring the radiograph. I said to them: "Look, you are giving a much bigger dose than you have to, and the question is how much more information do you get?" Later, it was shown mathematically that you could get more information for a given

dose by image reconstruction by CAT scanning than by X-ray tomography, and CAT scanning has become the standard method. Some people think that I should have got the Nobel Prize with Hounsfield. This story illustrates the important point in science that you sometimes find the solution to a problem from another field.

I have worked on about five major problems in my life. Each has taken about 10 years with overlaps between them:

- The structure and assembly of the tobacco mosaic virus (TMV);
- Spherical viruses and electron microscopy;
- Structure of transfer RNA (tRNA) and later an RNA enzyme (ribozyme);
- Chromatin and the nucleosome;
- Zinc finger proteins.

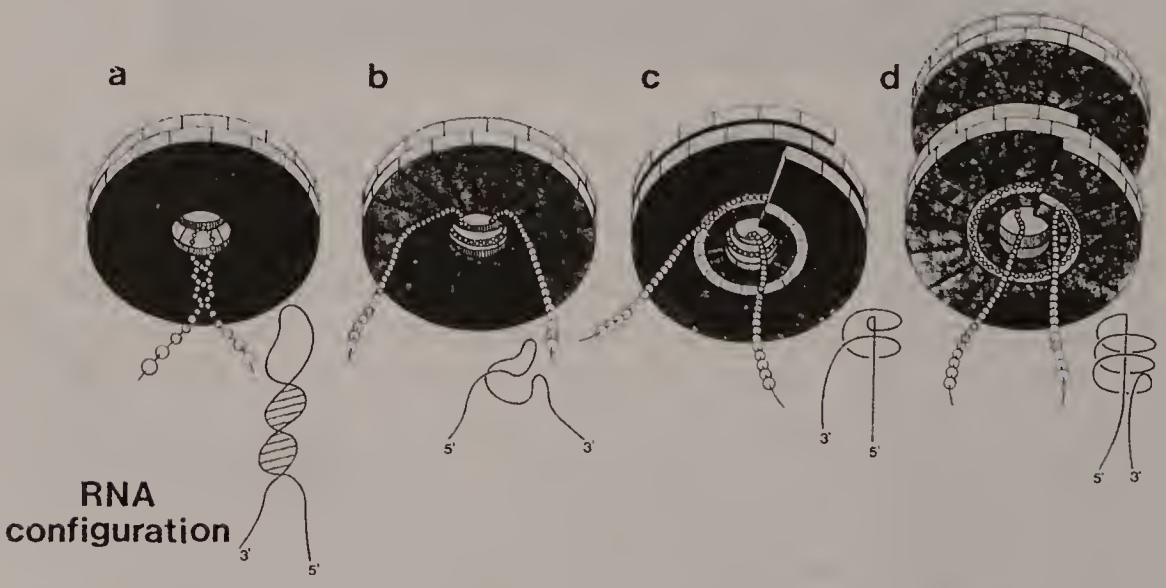
We were building a model of TMV in 1958 for the world exhibition in Brussels. The overall structure had been worked out by Rosalind Franklin and myself with Ken Holmes and John Finch. I showed the model in my Nobel lecture. Rosalind was in the hospital most of the time, and she died of cancer in March 1958. We did not know the exact shape of the protein subunit, and we had great trouble in building the model. An architect friend, who was building the model for us, built us a jig I had designed to start the helix, and I realized at that point that in order



Model of the tobacco mosaic virus (TMV) structure (all figures are courtesy of Aaron Klug).

to build such a structure, you need a specific nucleation event. There is a big difference between ordinary polymers and biological macromolecules. The key to biological specificity is a set of weak interactions. A polymer chemist could start building the model in the middle or at any other point. But for us, it was important to find the special sequence for initiating nucleation.

My Ph.D. work in the Cavendish Laboratory was on a problem of kinetics of phase transition in solids. There, one had to use a concept of the nucleation of the new phase. That was many years before, but something must have remained in my brain about nucleation. So I realized that in thinking about TMV assembly, you must separate nucleation and growth, and I identified in this disk-shaped protein structure (see below) the source of the nucleation. At the time, I thought that the end of the TMV RNA initiated the conversion of the cylindrical disk form of the coat protein into two helical turns of the virus. It turned out that the detail in this picture was wrong. Finally, we understood that the nucleation of the virus assembly is accomplished by a hairpin of viral RNA getting inserted into the central hole of the protein disk, between the two layers of the subunits. The RNA has a special sequence, which includes guanine repeats, and we knew that there were three bases for every protein sequence. So it was clear that it must be the nucleating sequence, and my colleagues Butler and Zimmern proved it.



Building up the model of the TMV structure.

A. N. Whitehead was a famous philosopher who coauthored *Principia Mathematica* with Bertrand Russell, and he said, "It is more important that an idea be fruitful than that it be correct." When I put together my Nobel lecture for publication, the editor wanted to cut out the picture depicting our initial idea of nucleation. He said it was wrong. I replied that it was indeed wrong in detail but everything essential was in there, so including it would show how science is a *process* of establishing the truth. The protein disk is an obligatory component for the formation of the virus. It performs two simultaneous functions. One is starting the physical assembly of the protein subunit, nucleation. At the same time, it recognizes a special sequence of the viral RNA, determining the specificity of interaction.

Many people think that science is just the application of various formulas. Some of it is, but they need to understand that, in a developing field, there are many steps on the way, and you can sometimes take the right step for the wrong reason. I worked on TMV from 1954, when I joined Rosalind Franklin, to the 1970s, when we were finally able to prove the mechanism of the assembly. Even after many years, this is the most detailed system of its kind that has been worked out. This was an important achievement, and for me, TMV was my first major scientific adventure.

A recent book review in Nature *contained the following remark about Rosalind Franklin: "... premature death can be a shrewd career move, for Rosalind Franklin became almost instantly a feminist numen."*

Yes, that is true. Because of an early death, you lose sight of the person. I knew quite a bit about Franklin's earlier DNA work, because she came to Birkbeck College straight after her DNA work, and she applied her experience in the DNA work to the virus study. After her death, I read not only her papers but her notebooks. When Watson's book *The Double Helix* came out, I had an advance copy and I decided to find out what she had actually done, because he wrote about her being an obstructionist. I saw that she had gotten very close to the answer, but most people did not know she had existed because her work had been lost sight of. Watson's book placed her very firmly as a protagonist in the story. It is very clear to me that if she had lived, she might have shared the Nobel Prize with Watson and Crick. That is what Watson thinks too. There would have been a dilemma for the Nobel Committee, because Wilkins had started the DNA work at King's and there can only be three people sharing the Prize. Now Rosalind was not Francis Crick, not as imaginative. But she

would have got the structure out in the end on her own. Crick and I have discussed this many times. One can see it from her notebooks, painfully working out the existence of two chains, in the **A** form running in opposite directions, but she had not grasped the relationship between the **A** and the **B** forms of DNA, which she had discovered. I have written about this. She would have solved it, but it would have come out in stages. For the feminists, however, she has become a doomed heroine, and they have seized upon her as an icon, which, of course, is not her fault. Rosalind was not a feminist in the ordinary sense, but she was determined to be treated equally just like anybody else. All the protagonists in Watson's book are portrayed with their failings, but the person who perhaps comes out worst in Watson's book is Wilkins. It was Rosalind's famous X-ray photograph that he showed Watson, but we must remember that in those days people were much more open. Wilkins and Franklin were very different personalities and didn't get on: if she had been a man, it would have been the same.

Of the major areas of your research, we have covered TMV.

Then there were the spherical viruses. Both Rosalind and I thought that I ought to develop a field of my own. The first X-ray pictures of spherical

A group of participants at the International Union of Crystallography Congress in Madrid in 1956: Anne Cullis, Francis Crick, Don Caspar, Aaron Klug, Rosalind Franklin, Odile Crick, and John Kendrew (courtesy of the LMB Archives).

virus crystals had been taken by Bernal and Carlisle at Birkbeck College, and there were still some crystals there. Donald Caspar had started at Yale on tomato bushy stunt virus. Crick and Watson had published a paper on the symmetry of spherical viruses and predicted that they must have the symmetry of one of the cubic point groups, but left it at that. Their work, however, inspired Caspar to get hold of some crystals of bushy stunt, and he came to the Cavendish Laboratory in 1955 and got some low-resolution X-ray photographs, which strongly indicated fivefold symmetry. Caspar had already become our colleague and friend because he had written an important paper on TMV. Caspar had provided the first one-dimensional electron-density map of the virus rod. Rosalind had solved the structure of the protein helix without the RNA. The two together showed that the virus rod had a hole down its axis and that the RNA was located in the middle of the helical protein array. Pauling said that this was all nonsense, that the virus could not have a hole in the middle. He was very magisterial, acting the great man. I was going to write a paper "on the role of the hole" in TMV because that is where, as I said earlier, the RNA enters during the virus assembly.

When Caspar came to Birkbeck, we looked in the refrigerator and we found crystals from the late 1930s. Caspar took the bushy stunt virus and I took turnip yellow mosaic virus. I knew that bushy stunt had a simpler unit cell, but Caspar was the first to begin the work so he had the first choice. John Finch and I showed that turnip yellow mosaic also had fivefold symmetry. Then, in 1959, Finch and I showed that the polio virus also had fivefold symmetry. This was important because people in those days believed that animal and plant viruses must be different.

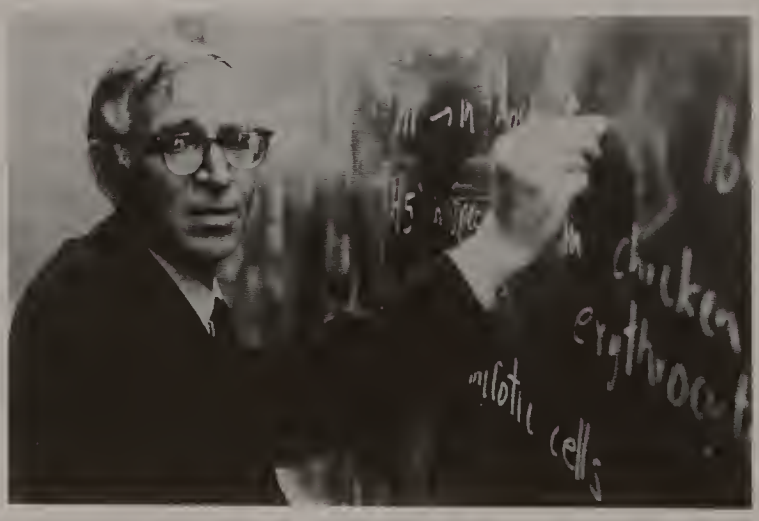
After we had published this paper, I received a letter from one of Buckminster Fuller's collaborators. He sent me a book with pictures of many geodesic domes. There was a controversy at that time about the symmetry of the protein shell of turnip yellow mosaic virus, which had been suggested to have statistical symmetry only, from the estimates of the number of the protein subunits. In the electron microscope, one could see 32 knobs and 32 times 5 is 160 subunits, which seemed reasonable. Our study showed, however, that this was not statistical symmetry — there had to be perfect icosahedral symmetry in the protein shell. We had the advantage of having protein-only crystals and also crystals of the virus with the RNA inside of the shell. I started thinking about the icosahedron and read the book, *The Dymaxion World of Buckminster Fuller*, written by Robert W. Marks. The book has a language of its own, but, in effect, I "translated"

it and realized that what Fuller was doing in his icosahedral domes was making small forced changes in the perfect geometry to accommodate more than 60 units. I realized that in the virus particle, one could automatically get approximate equivalence provided that the proteins or the contacts between them were flexible. I introduced the word quasiequivalence. Caspar made a cardboard model in which he also showed departures from perfect symmetry. So we got together and wrote the Caspar-Klug paper, "Physical Principles in the Construction of Regular Viruses" [*Cold Spring Harbor Symp. Quant. Biol.* **1962**, *27*, 1–24].

You were very eloquent in thanking Buckminster Fuller in that paper.

Yes. Although he did not understand the mathematics, he was stimulating. The mathematicians thought he was a crank, and the architects thought he was a mathematical genius. But I think that what Fuller was, was a Yankee Edison, a Yankee inventor, practical, totally untheoretical. I got to know him quite well. He said in one of his papers that he gave Caspar and Klug the mathematics. That is a joke, but I have great respect for him. He had read about the famous Euler formula and produced papers labeling the 2 in the Euler formula, $V+F-E=2$, as polarity with yin and yang, a total nonsense. The architects worshipped him, but some of the academics were rather snooty and snobbish. I made a BBC film with him.

When we proposed the idea of quasiequivalence, Max Perutz said in an interview in *Science* in 1966 that Klug was telling us these "most unlikely stories." Max kept quiet about this, and I saw it only later in print. At



Aaron Klug lecturing (courtesy of the LMB Archives).

that time, he thought that proteins were rigid and could not adapt themselves to different environments. On the other hand, our work depended upon the proteins having a certain degree of flexibility. Chemists have no problem with this now, but the physicists have problems with systems with many degrees of freedom.

The third entry on your list of major projects is the structure of tRNA.

That was at the time when studies of protein synthesis were at the forefront of molecular biology. The recognition of the genetic code was an important issue. Francis Crick was in the Lab, and he said we must find out the structure of tRNA, and we did. In one loop of tRNA, there is a codon that recognizes the code of the messenger RNA, the three bases specifying the amino acid. At the other end of tRNA there is the site of attachment of the amino acid. I was busy with viruses and TMV, but it was coming to an end for me. I could not be like Max Perutz, spending the greater part of my life's work on one thing, no matter how momentous.

Because of my experience with RNA in TMV, I was the only one in the laboratory with any experience on the properties and structure of RNA. My colleague Brian Clark was working on protein synthesis, and he was producing large quantities of tRNA. There are many different tRNAs, more than one for each amino acid, and we were the first to get crystals of tRNA.

As is often the case in science, it was a chapter of accidents. We all thought that it would be too difficult to crystallize tRNA and so planned to crystallize parts of the tRNA "cloverleaf" (the secondary structure). There was a man in Germany who said he could grow crystals of tRNA. It turned out to be all faked. But before I found out that it was faked, I thought, "If this man can crystallize tRNA, we should be able to do it." Later, others wrote a paper in *Nature* exposing him. I realized he was a phony, and I tell you how. When he came to our lab, we asked him about his crystals and he said they were lost on the ferry. But he described them to us as blue crystals because he used a copper solution to crystallize them. I asked him what sort of camera he used to take his X-ray pictures and he said it was a Guinier camera. I knew quite a bit about X-ray cameras and I knew he could not have recorded the low-angle reflections he was talking about and I told him so. He realized that I had trapped him so he said that they had built a special attachment! But his original claim was important for us in setting us to work on the tRNA crystals. So we

got our crystals and solved the structure and were in competition with Alex Rich at MIT, who had followed our first crystallization. Although they were the first in publishing, they published the wrong structure, having misinterpreted their map. Our work on the tRNA structure had important consequences for later work in that one of the metals binding to the molecule caused it to act as a metalloenzyme, which cleaved the RNA. This led me later to work on RNA enzymes (ribozymes).

Thus, understanding how metals bind RNA turned out to be important. This was scholarly work, which did not get into the headlines. But this understanding was very useful for ribozymes. In the meantime, I had abandoned the RNA work and moved to study chromatin. One of our referees on a visiting committee asked me, "How can you give up this tRNA work?" And I got a bad mark from him, but I pointed out to him that I wanted to tackle another major problem, the structure of chromatin. By this time, I had also given up electron microscopy, which by then had been established as a major addition to structural biology.

The first RNA enzyme we studied was, in fact, tRNA itself with a metal attached. We were using lead as a heavy atom, and we never could solve the structure. The reason, which we did not know at the time, was that the bound lead was cleaving the RNA. People had, in the meantime, found that some viral RNAs could splice themselves. John Dewan, an American postdoc, was a bioinorganic chemist, and I put him on this problem and our first paper appeared in 1983. We solved the structure of the uncleaved form of Pb-tRNA and the cleaved form. It showed very clearly how the lead atom was being held at low pH, where there were no hydroxyl ions around. Actually, I know some chemistry, strange as it may seem. At higher pH, the lead carries the hydroxyl ions so one gets base-catalyzed cleavage. We had some difficulties in publishing our report of this work, because one of the referees said that the turnover of the reaction here is only one per minute and enzymes work much faster than that. I had to explain to the editor that these things do not happen spontaneously — it may be only one a minute, but in the absence of the metal, the reaction would take years. The editor overruled the referee, but it was quite interesting to learn someone else's notion of what an enzyme is.

You mentioned chromatin as one of your major areas of research.

We worked on chromatin at different levels. The higher-order structure of chromatin was described in detail with nice diagrams in my paper for the

Welch Conference in 1985 [*The Robert A. Welch Foundation Conferences on Chemical Research. XXIX. Genetic Chemistry: The Molecular Basis of Heredity*, Proceedings Volume; pp. 133–160]. At this level of research, we did X-ray work on fibers, and you can learn a lot even about imperfect structures from X-ray diffraction.

At one point, in the 1930s, J. D. Bernal opted for studying more perfect rather than less perfect systems when he and W. T. Astbury divided their work along these lines, although he later regretted his choice.

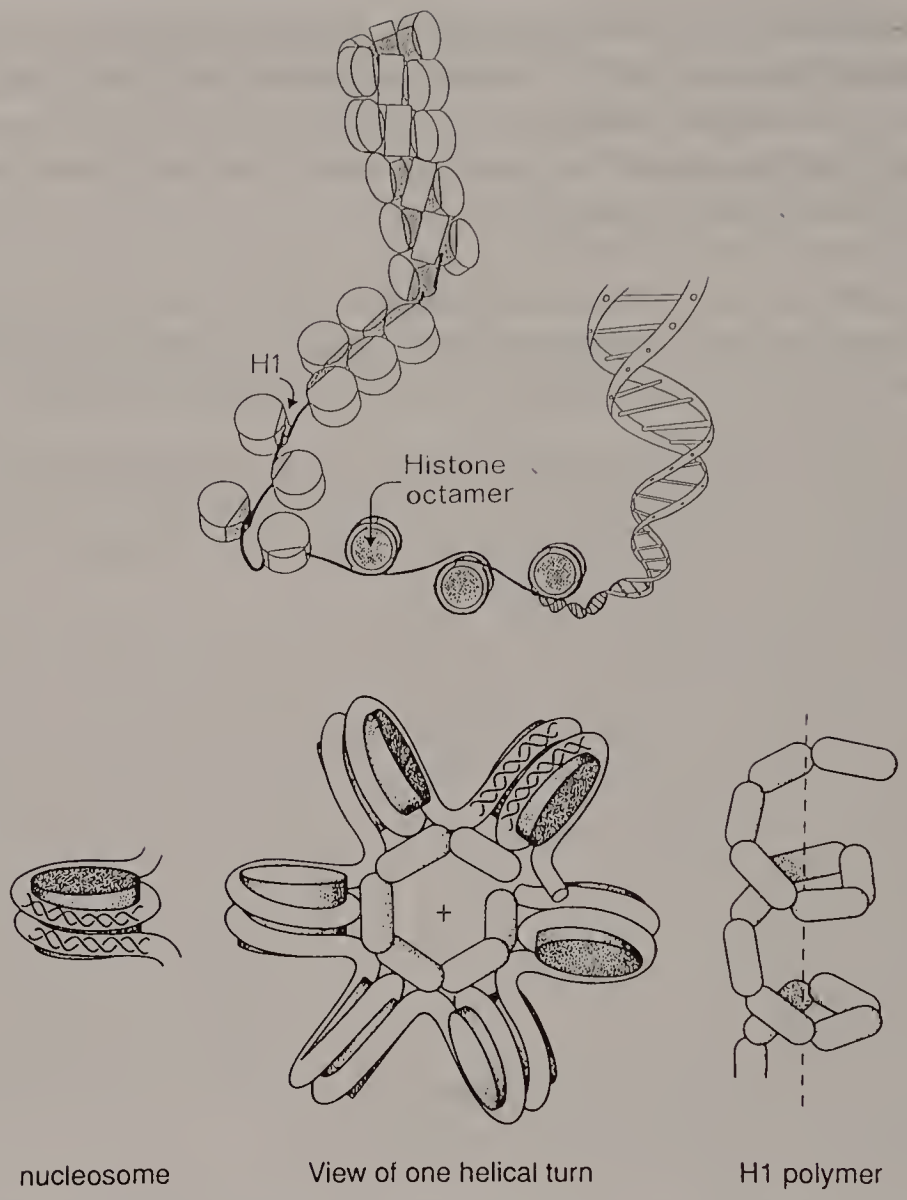
Bernal was right at the time because without the knowledge from the ordered structures, you could not interpret the fiber structures. It is also understandable that this choice bothered him because, in a sense, the ordered structures are the less interesting ones.

In the chromatin study, we also used X-ray solution scattering. We also produced crystals of the nucleosome and solved its structure to low resolution. Both were needed for interpreting the chromatin structure. The electron microscopy showed very little order. The genes that are not being transcribed are packaged in chromatin, so the bulk of DNA material is there. There is a hierarchic organization in chromatin (see, next page). The DNA is stored in the 300-Å-diameter fibers, which are further organized in loops. There are active and inactive units. What about the genes that are being transcribed into RNA? They are the ones being used for producing RNA, and they form the so-called active chromatin. In about 1982, I decided to begin the study of the structure of active chromatin by a combination of chemistry, biochemistry, X-rays, and electron microscopy.

You do not seem to have ever completely abandoned the metalloenzyme work.

I always wanted to follow up the work on tRNA and the RNA enzymes. There was another American postdoc, Bill Scott, who wanted to work on tRNA. But, instead, I suggested to him a real RNA enzyme. So we began working on a real RNA enzyme, the "hammerhead" ribozyme, and were able to solve its native structure and also capture various stages in the catalyzed reaction by fast freezing. I gave this up when Scott returned to the United States, and I became more embroiled in my zinc finger work.

We are gradually coming to my present interest, the zinc fingers. The American biochemists D. D. Brown and R. G. Roeder discovered that there

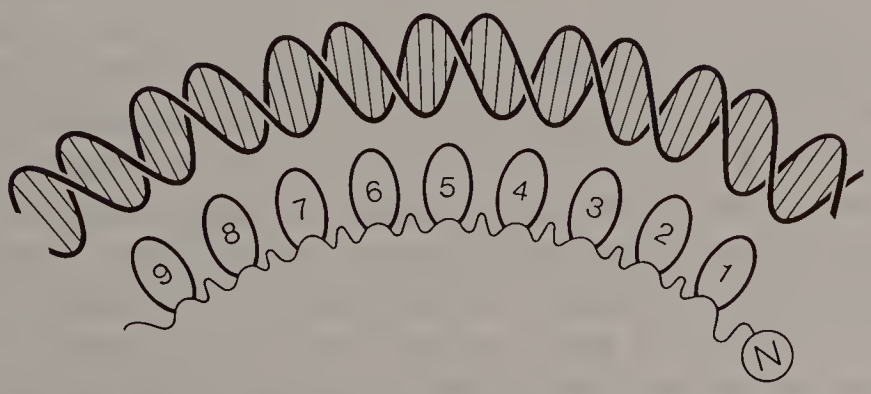


Chromatin: Hierarchy of the orders of folding.

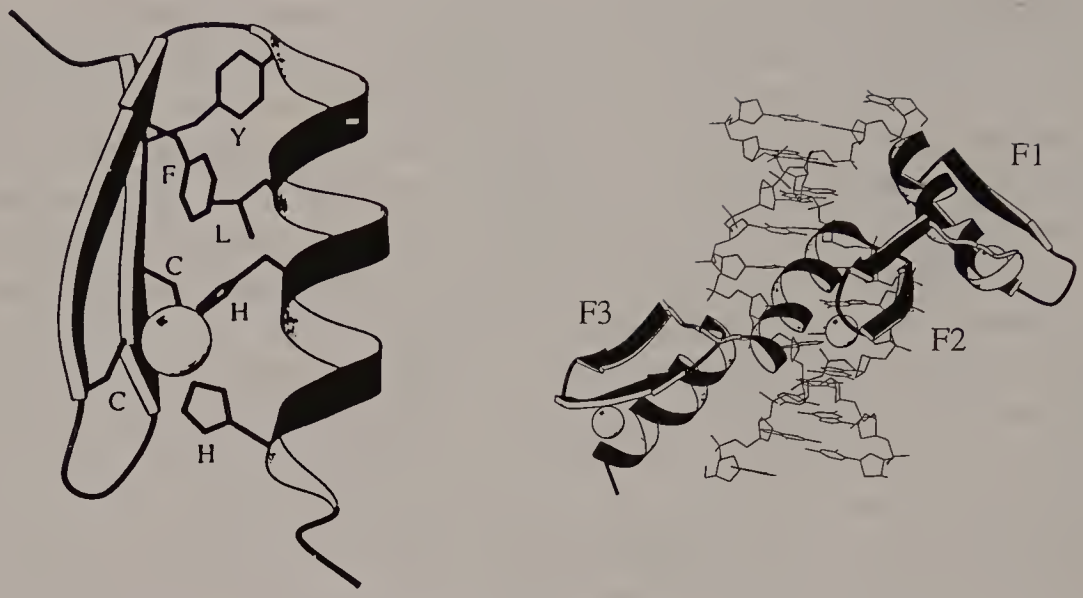
was a protein "transcription factor IIIA," or TFIIIA, vital for accurate transcription of the 5S RNA genes. It binds to a regulatory region of DNA. Switching on of a gene uses regions in it, called promoters or regulatory sequences, to which specific transcription factors bind that specifically recognize these sequences. A combination of these proteins switches on a gene, which means that they form a complex to recruit the polymerase, which copies the DNA into RNA. So this study was about the regulation of gene expression, not the mechanism of transcription.

I started out by hoping to find structures of the complex of proteins, which switch on these RNA genes. We started with one of them, the TFIIIA.

I put a bright research student from America, Jonathan Miller, on this project. At first, we could not purify TFIIIA. I realized that something must have been wrong with our protocol. But Brown and Roeder had succeeded. They were molecular biologists and were working on a scale of micrograms, using protein and DNA electrophoresis in gels, and not on the milligram scale of biochemistry. We wanted to extract the protein on a much larger scale for biochemical and crystallographic studies. Brown and Roeder were also adding chelating agents to take out metals, since metals will hydrolyze RNA and DNA. The protein also contained many cysteines so they used mercaptans for protection of SH groups. This was totally deleterious and the reason is very simple. The structure, which we discovered shows that this protein has repetitive elements in it, nine repetitive elements. Each repetitive unit contains two conserved cysteines and two histidines, and these are well-known ligands for the metal zinc. They also contain conserved tyrosines or phenylalanines and other aromatic hydrophobic amino acids, which form a hydrophobic core. So there were repetitive zinc-binding domains in this transcription factor. The notion of repetitive units in the model came from cleavage experiments with proteolytic enzymes. Ultimately, other people and ourselves have shown our model to be correct by 2D NMR and by X-ray crystallography. We called the units zinc fingers because they are stabilized by zinc and grip or grasp the DNA. It is a modular system, and this was a new concept. In such a system, each finger recognizes a short specific sequence of DNA, and these different fingers can be combined to produce a larger DNA-binding protein domain. There is a combinatorial principle at work here, within a given protein.



The original zinc finger idea: Representation of the nine zinc fingers binding to DNA; the binding mechanism was not yet known.



A single zinc finger and three zinc fingers binding to DNA.

The single finger is the module, and it is a stable unit. The individual fingers are joined in a flexible way. Each finger can have chemical distinctiveness, the same structure but with a variation of the particular amino acids that contact and recognize the DNA. This work took us many years, but when you discover something new, many others begin working on it, and that spoils the fun.

In studying the rules of recognition, we did not systematically change the amino acids one by one to make a strong binder to DNA. Rather, we used the phage display method of chemical combinatorics, which we did not invent but we adapted it for the zinc fingers. We made a library of 6 or 7 million variants in the finger recognition site and applied a selection process to pick out the strongest binders for a given DNA target. At the end, we had the specific zinc fingers for binding DNA and tested them by a reverse experiment, that is, by randomizing DNA and seeing to which DNA sequence the finger bound preferentially. This was physical biochemistry rather than molecular biology. Going from *in vitro* experiments to real systems, we designed a protein *de novo*, which bound to a sequence of an oncogene, a cancer gene, and switched it off when present in a mouse cell line. We can now design proteins, using zinc fingers that can combine with desired DNA targets. Of course, what we put into the cell is not the protein, it is the DNA construct used to transfect the cell.

I have given a concentrated account of 50 years of scientific research. Now I have a small group of five people, a student, a visitor, a technician, and two temporary associates. I have to concentrate on a few things. I am a "retired worker" in MRC parlance, I have a small office and a lab upstairs. A European Union grant supports my oncogene research.

Can we go back to the very beginning of your life?

My father and mother lived in Lithuania when I was born in 1926, and when I was 2, we went to South Africa, where members of my mother's family had emigrated in about 1900.

Have Lithuanians ever claimed you as their Nobel laureate?

No, but the Soviet Academy of Sciences once did, because Lithuania was, after 1940, part of the Soviet Union. But when I was born, Lithuania was an independent country. My father's family lived on a farm, and my father's father was a cattle dealer who owned land, which was unusual for Jews. When the Russians occupied Lithuania in 1940, my uncle, who had inherited the land, was deported to Siberia as a bourgeois. One of his children disappeared, and the others were killed by the Germans. Some of the Lithuanians were actively helping the Germans. One of my cousins was killed in the Red Army, another as a partisan. I do not have the complete story, but nobody among the family survived.

My wife Liebe is also from South Africa. She is a choreographer and used to run a modern dance group in Cambridge. Later, she took a training course in psychotherapy and worked for the University Student Counseling service, and she is now semiretired. We have two sons. Both are academics; one is an economic historian in Israel, and the other is a physical chemist at Imperial College.

I am a professing Jew and I go to the synagogue sometimes, but not as often as in earlier years. I grew up in South Africa and had a relatively free life. There was anti-Semitism in South Africa but not so much. We grew up in Durban, where there were very few Jews, a few hundred families only. My elder brother and I were the only Jews in our primary school, and there were one or two bullies who would occasionally pick on us because we were Jews. The biggest bully must have learned it from his parents since we must have been the first Jewish boys he had met. When my brother and I were together, we would fight back, but if either of us was alone, they would on rare occasions set on us. Some other boys

sometimes stood up for us, so I learned some lessons early on. That was regarded as normal then in South Africa. But here, in Britain, I have encountered no anti-Semitism to speak of.

What turned you to science?

In my last year at school, I read a book by Paul de Kruif called *Microbe Hunters*. So I started in medicine at the University of Witwatersrand in Johannesburg as a way to microbiology. Gradually, I became more interested in biochemistry, gave up anatomy but continued in physiology, biochemistry, and histology. My parents were not pushing me in any direction and left me to decide. Eventually, I switched from medicine to science and moved to chemistry and also to physics and mathematics for my B.Sc. degree. Then I moved to the Physics Department at the University of Cape Town, where I took an M.Sc. degree under Professor R. W. James.

James had been a colleague of Lawrence Bragg in Manchester, and I learned a lot from him, from the way he clearly set out a problem. I wanted to understand quantum mechanics, wave mechanics, relativity, and similar areas. My research was on small-molecule crystallography. We had to build our own apparatus, and I built a microdensitometer to measure the densities of spots on X-ray diffraction photographs. Then I went to Cambridge because Cambridge was the place to go, and I taught myself quantum chemistry in preparation. I did not quite know what I wanted to do but had some idea that I wanted to do some nonorthodox crystallography. But Bragg would not allow this. He was the head of the Cavendish Laboratory and he wanted me to work on silicates. He told me that the MRC unit, where Perutz was working, was full. But I did not have any strong feeling about any particular branch. Some people know exactly what they want to do from the very beginning; I did not. I was just wandering about. Then, after my Ph.D. and a year in the Colloid Science Department in Cambridge, I went to London on a Nuffield Fellowship and, by chance, met Rosalind Franklin.

Are you an insider in British life?

I was not until very recently. Yes, I think, I am an insider now, by virtue of the Royal Society. If it is a question about how much one influences people, one inevitably meets a lot of people at the Royal Society, and some of them are influential. Then, we have to deal with the government. We produce reports, papers. It's a lot of hard work. I am nearing the end

Aaron Klug with the Emperor of Japan at the Royal Society (London) (photo courtesy of Aaron Klug).

of my third year as President of the Royal Society, and the term is for five years.

Does the British government take the advice of the Royal Society?

Sometimes.

About questions like the mad cow disease (BSE)?

We publish reports and responses to parliamentary and other enquiries. We published a report on genetically modified plants, the best study there was at the time on the subject. In the Royal Society, you can get a group of scientists together and everything is done for free, nobody gets paid, including the President.

For the GM (genetically modified food) report, I was a member of the group. We looked at the different regulations and saw that there were many regulatory bodies but no one was looking after the whole picture. We learned this from the days of BSE, which was a much more pressing problem, that there were many organizations dealing with the problem, but no coordination. Now the government is acting on this.

We give advice whether asked for or not. We are in effect the Academy of Science of the United Kingdom, but we draw our Fellows from the whole Commonwealth, since we include India, Canada, and others. Currently, one fourth of our Fellows work abroad.

Would you care to comment on Russian science?

It is terrible to see it collapsed. It was strong in physics and chemistry but the biological sciences never recovered from Lysenko. The Royal Society had a scheme of helping Soviet science and got a special sum from the government to try to do so, but it was not on a large scale. We help individual scientists. Some come here. But the way the whole thing has collapsed is a tragedy.

Quite a few great British scientists have left the country, like Crick, Brenner, Dewar, Barton. Would you care to comment on this?

Crick left because he was reaching the age of retirement at MRC and he had been offered a very good position in the United States with no limit of tenure. He is still active at well over 80 and at the MRC he would have had to retire at 65. It was an ill-advised policy, which is relaxed now. Brenner went to the States more recently. In this country Max Perutz was the first former head of an MRC laboratory to stay on in the same lab.

I would like to ask you about science and nationalism. When Harry Kroto won the Nobel Prize in 1996, I saw a headline, "Kroto scored one for Britain."

That happened only recently; in the earlier days, people paid little attention to the Nobel Prize in this country. It was not like on the Continent, where these things were regarded as terribly important. When Britain ran an empire, they did not think much of science and just took it for granted that it was of high quality. These things seem to count for more since Britain has become a moderate-size European nation.

Do you have a stand on human cloning?

I am against it now. A Royal Society paper has called for a moratorium on any embryo experiments beyond 14 days. That fitted in with earlier

legislation on embryo research, which was drawn up with input from the Royal Society. The notion of cloning a human being is personally rather abhorrent to me. It is hard to say why, rationally.

You are a member of the Order of Merit and President of the Royal Society. Is there anything more you could have achieved?

I do not think of it that way. I did not enter a race; I entered science out of curiosity. I do not think I could have done more and would not want anything else anyway. I am trying to keep my research group going, and that is my main scientific interest. There are times when I almost resent having to go to London for about two days a week, to promote science in various ways, but it is my duty. Various people told me that it was my duty to undertake the Presidency; I had turned it down five years previously when I felt I could do more for science at the Laboratory of Molecular Biology.

Who are your heroes?

I do not have heroes and never had any. Of course, I marvel at the mind of the Einstein of 1905, to create relativity and so much else. There are certain people I admire enormously, like Francis Crick, and I learned a lot from him.

Any hobbies?

I read and read quite widely. I read ancient history and collect Greek and Roman coins. I cannot afford the more expensive ones but look out for affordable ones with historical connections. I have also begun to collect old Jewish coins from the Hasmonean times and also from the Roman procurators.

At the turn of the century, would you care to look back on the science of the 20th century?

The general view of science is that science has been a rather bad thing. People only think about the harm it is doing, and we have a big backlash against it. People forget the benefits it has brought. People often confuse science and the application of technology. However, in the end, things like nuclear energy will just be inevitable, unless solar energy proves practical.

Would you agree that the two main areas of success of science in the 20th century were nuclear physics and molecular biology?

I think so, yes, it has to be. Quantum physics and atomic energy and molecular biology. But, in fact, molecular biology is now a set of techniques and approaches, and it will become part of biochemistry and genetics. It was historically very important for molecular biology to define itself. Sometimes you have to define yourself *against* what exists. When I was a research student in the 1950s, the biochemists never thought in terms of DNA transmitting information. They thought of proteins as the molecules of life. This is why it was important to use another name. It is like religion in a way. You had to define the Protestant religion against the Catholic during the Reformation. Eventually, molecular biology will be absorbed into biochemistry.

There is a notion that we are living now in a post-molecular-biology era.

There is probably some truth in that because molecular biology is now all-pervasive; the biochemists and cell biologists now do molecular biology, and ever since the development of the polymerase chain reaction (PCR), all the medical people can do some molecular biology. Every medical student can now clone a gene.

Would you venture to say what the next frontier will be?

That is fairly obvious although I do not know how long it will take, but neuroscience, the workings of the nervous system and particularly the brain. If I were starting over again, I probably would go into neurobiology. Whether I would have the taste for those kind of experiments, I do not know, but I find neural networks fascinating.

My scientific life has been one in which I worked on relatively messy systems, which physicists would not touch. On the other hand, I was able to bring some rigor into them by doing things properly and by developing new techniques, and it suited me very well. Those of us here in the Lab have helped create the subject so it bears our image. But now cell biology has become so important, and I do not know whether you can make any progress with the brain without finding out more about the interactions between sets of molecules. One just has to start.

Thinking about science, you have to start even though you do not know where the end will be. I have been lucky because I had a good preparation without planning it and started my career when a new subject was opening up here and have had the opportunity to work for the MRC. This is a very enlightened body, which has let me work on long-term projects. Research is not just going from mountain top to mountain top, you also have to work in the valleys, and that takes time and freedom.

John T. Finch, 2000 (photograph by I. Hargittai).

21

John T. Finch

John Thomas Finch (b. 1930 in England) is Emeritus Member of the Scientific Staff of the Medical Research Council Laboratory of Molecular Biology (LMB) in Cambridge, England. He received his B.Sc. degree (Special Physics, 2.1) from King's College, London in 1954 and his Ph.D. (Biophysics) from Birkbeck College, London in 1959. He was elected Fellow of the Royal Society (London) in 1982. His thesis work was on X-ray diffraction studies on viruses (tobacco mosaic virus, turnip yellow mosaic virus, and poliovirus) in Rosalind Franklin's group, taken over by Aaron Klug after Franklin's death in 1958. Since 1960, Dr. Finch worked on the X-ray diffraction and electron microscopy of viruses, tRNA, chromatin and nucleosome core, ovalbumin, and DNA-protein complexes in Aaron Klug's group in the LMB, until his retirement in 1995. We recorded our conversation on February 8, 2000 in the LMB, Cambridge. My first question was about his education and start in research.

I was born in London and went to local primary and secondary schools and from the latter I won a scholarship to King's College, London, and took a special physics degree. Although I went to talks arranged by the college physics society, I can't remember much about them, and the exciting research going on at that time (1951–54) did not make much impression. I can remember Rosalind Franklin who must have spoken on DNA, and talks on collagen with striking electron micrographs. At the end of the course, I was interviewed by Maurice Wilkins to find out what I wanted to do, and though I wanted to get into the biological/biophysical field, there was no offer to join the biophysics group at King's.

I can't trace back the origin of my interest in science, but my interest in the biological applications of physics was probably promoted by the research talks I heard at King's, though it may have originated from a long stay in hospital with tuberculosis of the spine, before going to King's. During that illness I had a lot of time to read, and read as much popular science as I could get hold of. (I also tried to get onto a *Nature* circulation list, but nothing came of that — I suspect the hospital people thought it was one of the nudism magazines that were around then.) Following graduation and another hospital stay, I began looking for a job, and saw that Rosalind Franklin, who by that time (1955) had left King's and was in Bernal's crystallography department at Birkbeck College in London, was advertising for an assistant in her work on the structure of viruses. So, I applied and was engaged.

Rosalind's lab was an attic room at the top of 21 Torrington Square — one of a few remaining houses in the bombed remains of a Georgian terrace. I was housed in the adjacent attic room with Aaron Klug, who was working with Harry Carlisle's ribonuclease group. I remember being introduced to Bernal by Rosalind on my first day. She had just written her first paper on tobacco mosaic virus (TMV) in which she referred to the length of TMV recently established by electron microscopy. Some earlier collaborators of Bernal in his virus work, Bawden and Pirie at Rothamsted Plant Experimental Station, did not believe this result and condemned Rosalind for citing it. They were both very influential in the Agricultural Research Council who were funding Rosalind's work and I suspect this did not help when her grant was not renewed.

Rosalind Franklin (1920–1958), photograph by Henry Grant, AIIF (courtesy of the Medical Research Centre, Cambridge, England).

My first project was on TMV. In her DNA studies, Rosalind had done a lot of work on the water uptake of DNA fibres and she wanted to do the same for TMV. She prepared the virus and I aligned it using the Bernal–Fankuchen technique of drying from a dilute solution against a fixed meniscus. I then took X-ray diffraction photographs and calculated the interparticle spacings for specimens equilibrated against particular relative humidities. The experiment was not very successful as my method of determining the relative humidity was not sufficiently accurate.

Later in 1955, Ken Holmes joined the group, and we were both made Ph.D. students, with Bernal as official supervisor since Rosalind held no university appointment. Ken took over the work on TMV gels while I concentrated on spherical viruses.

Watson and Crick were also interested in the virus work. Watson had taken X-ray pictures from TMV just before the DNA structure was established hoping to get the RNA structure in the virus, but this did not prove successful. After the DNA work, they became more interested in the small spherical viruses because they promised better results than the rod-shaped TMV.

Bernal's group had obtained X-ray powder photographs from the small spherical viruses tomato bushy stunt (TBSV) and turnip yellow mosaic (TYMV) just before the war in 1938. These had shown that the unit cells were both cube-shaped. From the sizes of the cells and the virus particles, there was only one virus particle per lattice point, and so if the crystals really had cubic symmetry, the virus particles would be cubic too and would have to be composed of identical subunits. At that time, Don Caspar joined the MRC unit in Cambridge. He had previously X-rayed TMV and located the radius of the RNA, and was keen to X-ray spherical viruses too. Caspar came to Birkbeck, where the powder work had been done. By then Aaron Klug had begun collaborating with Rosalind on the virus work. In the refrigerator at Birkbeck were single crystals of both TBSV and TYMV, and they were divided out, TYMV stayed with the group at Birkbeck TBSV went with Caspar to Cambridge. Caspar took X-ray precession photographs and showed that it had cubic symmetry and evidence for icosahedral symmetry. I was left with TYMV — the main subject of my thesis work. The X-ray pictures also indicated icosahedral symmetry, although not so clearly as for TBSV as the virus was present in two different orientations in the crystals.

Then Rosalind was brought some crystals of poliovirus from the U.S. and I photographed them at the Royal Institution. I remember that she

was amused that the customs people at the airport were a bit diffident about letting in poliovirus, until Patsy Schwerdt, who brought them, told them that it was crystallized and they were then quite happy — presumably by analogy with crystallized fruit being no longer functionable. Rosalind tried to take an X-ray picture of the sample at Birkbeck, but there was a lot of feeling against this being done there — particularly as one of the people there had suffered from polio. The staff did not think that the lab was equipped for dealing with such infectious agents.

From the safety aspect, the Royal Institution was not any better equipped for this kind of work, but the Director was Sir Lawrence Bragg who was very interested in the work. The crystals were transferred to the School of Hygiene and Tropical Medicine — across the road from Birkbeck — and Aaron wrote out a protocol, which satisfied the local safety people as well as the Royal Institution. So I mounted the crystals in the School of Hygiene and Tropical Medicine, watched by Aaron (part of the protocol) and took them to be X-rayed at the Royal Institution. They had a more powerful X-ray tube there — a copy of the Broad rotating anode tube designed for the MRC unit at the Cavendish Laboratory in Cambridge — but the diffraction was weak and the runs were fairly long, sometimes overnight. We kept the crystals cold by blowing air through an ice/water mixture and then on to the crystal — the ice did not last very long, so someone had to be there all the time. I remember finding the Royal Institution quite an eerie place during the night, with busts of past directors in the windows lit from the streetlights outside. We succeeded in getting X-ray pictures from the polio crystals and saw again the evidence for icosahedral symmetry in the patterns.

Was there any reference in your conversations with Rosalind Franklin to her previous work on the DNA structure?

Yes, Gosling used to come to Birkbeck. I don't think she was allowed to go to King's and I think they were banned from doing any work, but she had to write up the work she had done there.

Banned?

Banned from going to King's. I think Randall didn't like the idea of Gosling still being supervised by someone who was not in the King's labs. There was possibly not an official banning but effectively it was so. That was definitely my impression.

There was no male/female separation at Birkbeck. There was a Senior Common Room and a sort of "High Table" room where senior staff lunched separately from the rest of us, Rosalind with them, that is, with the senior staff.

How often did you see Bernal?

Bernal traveled a fair bit — he wasn't there every day to discuss things. Even when he was passing through the lab he would shoot by quickly to his flat at the top of 22 Torrington Square, over the crystallography rooms. It was only by chance that you saw him sometimes. He would poke his head in through the door and ask "Anything new?" and if you didn't grab his attention in the first five seconds he would withdraw and continue on his way.

I only saw him once doing a practical experiment while I was at Birkbeck, and that wasn't too successful. He was trying to examine a crystal on a small rotation camera, but plugged in a 230 volt lead into the 6 volt light socket — there was a loud bang and much smoke and Bernal gave up and stalked out.

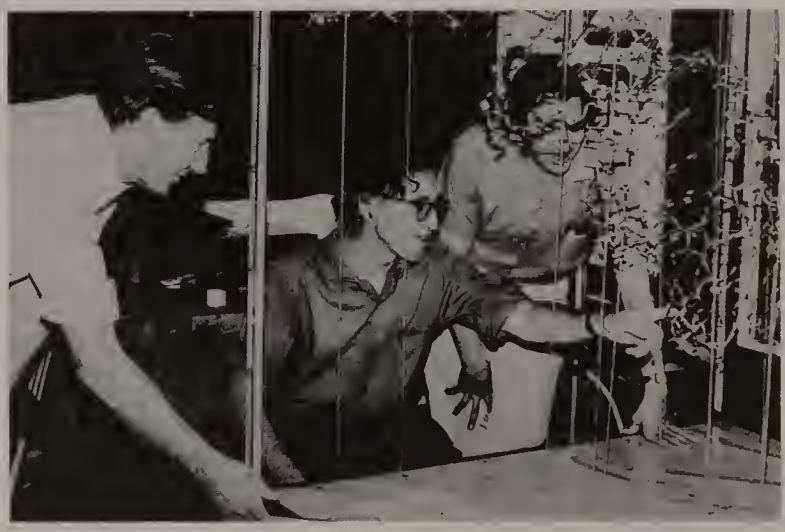
I knew very little of Bernal's private life. I remember when Bernal was invited to give a Friday evening discourse at the Royal Institution. On such occasions they usually invited the speaker's wife as well. It was while I was taking X-ray pictures there and I had a message to see Bragg in his flat at the top of the Royal Institution. He felt he should invite Mrs. Bernal, but wasn't sure if there was an official one, and wanted to make sure before sending the invitation. So, I confirmed at Birkbeck that there was an official Mrs. Bernal and she was invited.

Rosalind died in 1958 and I remember taking photographs of her lab as she left it — it seemed to me worth keeping as a record. Aaron took over the virus group and became the *de facto* supervisor of my thesis work, although the legal one remained Bernal. I completed my thesis in 1959 and submitted it to Bernal who insisted on a reference to Euclid regarding the icosahedron. John Kendrew was the external examiner.

For further structural work we needed more X-ray photographs. At this stage we were already being funded by the Medical Research Council and Aaron had been invited to join the new LMB in Cambridge. I came up a bit earlier to try to get X-ray pictures on the rotating anode tube in the Cavendish. This was in 1961 and in 1962 came the move into the LMB.

Soon after coming to the LMB, I began electron microscopy. Purification of viruses was an important task in the virus lab, and one easy way of

Rosalind Franklin's office at the time of her death in 1958, Birkbeck College, London (photograph and courtesy of John Finch).



John Finch, Aaron Klug, and Brian Clark at the Laboratory of Molecular Biology in Cambridge, England, 1974 (courtesy of the LMB Archives).

monitoring purity was by electron microscopy. Hugh Huxley had arrived by this time and had microscopes for his muscle work, and he thought that as we produced so many samples, we had better learn how to use the microscopes ourselves. I became interested in this and started taking

photographs for structural information. The first viruses I looked at were the small plant ones we had been X-raying TBSV, TYMV, and TCV (turnip crinkle virus), and we were able to determine the subunit arrangements on these.

We then became interested in the human wart virus, which showed the first skew arrangement of subunits ($T = 7$). Bragg, when he visited us was particularly interested in this as his daughter had suffered badly from warts at one stage. A doctor had advised stroking them with a feather every night, and they had vanished after a bit and Bragg was curious as to why. Well, we had no structural explanation, but apparently many cases of warts clear up spontaneously, and presumably the feather gave this a chance to happen — for the same reason, we were told, the wart clinic in Cambridge had a built in delay in their appointment system.

I don't think I would class any one of the projects I've been involved with as above all the others — each seemed to have its own excitement. Many of them have involved low resolution work — disentangling the structures of icosahedral viruses from the electron microscope images of negatively stained specimens, for example, and the neutron diffraction work on the nucleosome — being equally divided between protein and DNA, it was ideally suited for contrast matching. The tRNA crystals obstinately remained low resolution for a long time, until the well-ordered crystals of yeast-phenylalanine were grown.

What are you engaged in nowadays?

In science, I have been collaborating with a group in Utah, investigating the structure of the HIV core — the nucleocapsid. By electron microscopy we have found that the proteins making up the core surface are arranged with hexagonal symmetry, which explains how this core particle adopts a conical shape in the complete virus particle. Like the simple icosahedral viruses the curvature is induced into the basic hexagonal net by introducing twelve pentamers, but instead of being distributed uniformly as in those viruses, they are split into five at one end of the core and seven at the other and produce the conical shape.

As well as that, I am writing a "family" history of the Laboratory. There is much to write about and hundreds of photographs to accompany, and hopefully will make an interesting collection.

Sidney Altman, 1998 (photography by I. Hargittai).

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Sidney Altman

Sidney Altman (b. 1939, in Montreal, Canada) is Sterling Professor of Biology and also Professor of Chemistry at Yale University. He shared the Nobel Prize in Chemistry for 1989 with Thomas Cech of the University of Colorado at Boulder "for their discovery of catalytic properties of RNA." Since his graduate studies, Dr. Altman has been concerned with the biochemistry of nucleic acids and with the genetics of tRNA expression.

Sidney Altman got his B.S. degree in physics from the Massachusetts Institute of Technology in 1960 and Ph.D. in biophysics from the University of Colorado at Boulder in 1967. He did postdoctoral work at Harvard University and at the Medical Research Council Laboratory for Molecular Biology in Cambridge, England. He has been at Yale University since 1971.

He is Member of the National Academy of Sciences of the United States (1990) and the American Academy of Arts and Sciences (1988) and recipient of the Rosenstiel Award of Basic Biomedical Research (1989), the National Institutes of Health Merit Award (1989), and has numerous other distinctions. He served on the Board of Governors of the Weizmann Institute of Science (1990–1995) and as President of the Yale Hillel Association (1995–1997). His other past and present positions include memberships of scientific advisory boards of biomedical companies and research funds.

I recorded our conversation in Dr. Altman's office in the Department of Biology of Yale University in New Haven, Connecticut, on May 19, 1998.*

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Looking back, how would you summarize the research for which you were awarded the Nobel Prize in Chemistry in 1989?

First of all, the discovery of catalytic RNA was completely serendipitous in our laboratory and, I believe, in Tom Cech's lab, too. My work grew out of my postdoctoral experience.

I was very fortunate to do a postdoctoral stint at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, England. It was there that I started working on transfer RNA (tRNA). I was supposed to work on physicochemical methods of studying the structure of tRNA because it had not yet been crystallized when I was accepted at the MRC. However, when I showed up in Cambridge in 1969 and spoke to Sydney Brenner and Francis Crick, who were joint heads of this unit, it turned out that tRNA had just been crystallized a few months beforehand. In a sense, the project I was supposed to work on became pointless. They told me to think of something else to do and they gave me a few days to do just that. I decided to search for and examine acridine-induced mutants of tRNAs.

The acridines are planar, aromatic molecules. That enables them to intercalate between the bases in DNA, which are also planar, aromatic molecules. The acridines produce frameship mutants in DNA; that is, they make deletions and additions of bases in the nucleotide sequence of DNA. The mechanism is more or less understood: the acridines intercalate into DNA during replication and induce the errors. Those kinds of mutants had not yet been made or studied in tRNA. My idea was to mutate a tRNA gene with an acridine compound and thereby to make deletions or additions in the tRNA that should produce changes in its conformation in solution. By conformation I mean a stable, folded structure of the macromolecule in solution. tRNA has a very tightly folded structure with a lot of tertiary interactions. Besides hydrogen bonding that mediates the formation of the standard Crick-Watson helices in tRNA, there are other kinds of hydrogen bonding and other kinds of weak interactions between distant parts of the molecule that stabilize its folded structure in solution. Presumably, if one removed a base from or added a base to the nucleotide sequence, the canonical structure would no longer be able to form.

How far ahead was DNA sequencing by the time you were doing this research in Cambridge?

Sequencing RNA was already well established, and I learned the technique in the laboratory there. When I first saw somebody run through the whole Sanger procedure for sequencing RNA, I thought it was magic. I thought it could not possibly work. But it worked beautifully all the time. That was so impressive about Sanger. He developed these simple, elegant methods for sequencing. At that time he was working on DNA sequencing, but he had not yet developed the dideoxy method.

I made the acridine-induced mutants of tRNA, and they had peculiar genetic properties, which I didn't understand. I reasoned that the molecules encoded by the mutant genes would be highly unstable *in vivo* because they were deficient in some way. They weren't normal tRNAs.

For historical purposes I mention that I had a one-year fellowship at the MRC Lab in Cambridge. The experiments I just described were done in June 1970. My fellowship ran out at the end of June. I was desperate. I had no job and I didn't know what I was going to do. Then I did the experiment to look for the unstable transcripts of the mutant tRNA genes. About two or three weeks before I was supposed to leave the MCR Lab, I did an experiment, which clearly demonstrated that the transcripts could be isolated and that they had certain interesting properties. I just took off from there.

When I isolated a radioactively pure transcript of a mutant tRNA gene and exposed it to an extract of bacteria, it was obvious from the first experiment that there were enzymes in bacteria that cut off both "extra" ends that were not part of the mature tRNA sequence. In fact, there had to be several enzymes involved in the "processing" of transcripts. Nucleic acids have a distinct polarity, and the enzyme I focused on was the one that processed the 5′-end tRNA transcripts accurately. That enzyme was ribonuclease P, or RNase P. I worked on it for another year at Cambridge after Crick and Brenner decided to support me for a while from laboratory funds.

Brenner and his colleagues had done a classic study of mutants of tRNA before I got to the MRC. They had made mutants by treating the DNA coding for these tRNAs with various chemicals that induced base substitutions, not deletions or additions of bases. They used agents that resulted in a change, for example, of an adenine into a guanine. There are various agents, like alkylating agents that produce those kinds of mutants. So Brenner and Crick figured that there was nothing new to learn about the mutants of tRNA. But the acridine-induced mutants worked through an entirely

different chemical mechanism and produced different kinds of mutations in DNA and proved to be very interesting.

To what extent does acridine change the nucleic acid? Does it build itself into it, or is there only a loose connection?

The acridines I used do not become covalently linked to DNA. They slip in between bases in the DNA double helix and are held there by stacking interactions of circulating π-electrons in a noncovalent fashion. They intercalate. They look like an extra base in the nucleotide sequence. When DNA Polymerase comes along to replicate DNA, it makes a mistake. Sometimes it puts in an extra base, sometimes it skips a position when it encounters an acridine.

So the mutant is a result of mistakes in the copying process in the DNA.

Exactly. And then the "mistake" is passed on to the RNA, which is an exact copy of the mutant DNA.

Coming back to my story, after my second year at Cambridge, I came to Yale. I thought that it would be an interesting project for a graduate student, to purify the enzymatic activity we had found in bacterial extracts and to characterize it. It's a perfectly straightforward project. I did give this to a graduate student, Ben Stark, who worked very hard. It turned out to be extremely frustrating.

Ben would purify the activity to a certain extent and it would seem to become very unstable, very hard to purify further. He would run the enzyme activity in a gel and stain for proteins. His initial characterizations showed no proteins. But when Ben overstained the gel for RNA, he found some RNA bands. So he said, "This enzyme is made of RNA, not protein." To which I replied, "That's foolish." I asked him how many cells he started with, and it was a very small amount, 5 grams. I suggested that he start with 500 grams. He did and he reran the purification and stained his gel again for protein. Now there were some protein bands visible, but when he overstained the gel (since he still believed in the RNA observation), the RNA bands were still there. I thought that if we purified the enzyme further, we would get rid of the RNA. (The time is now around 1975.) Ben purified the enzyme further and got it down to one band of protein. But he also found that there was one particular species of RNA that co-purified with the protein. It just didn't go away. The experiment that

he did to convince me that the RNA was needed was to treat the highly purified enzyme with a separate ribonuclease, micrococcal nuclease (MN). MN requires calcium for its activity. The activity that we were interested in required magnesium. Ben pretreated the enzyme preparation with micrococcal nuclease. Then he took the calcium away with a chelator of calcium ions and showed conclusively that if we treated the RNase P with MN, it lost activity. He also showed that he was destroying the RNA that purified with the enzymatic activity. That was the evidence that RNA was an essential part of the enzyme. If we also treated the enzyme with a protease, the activity vanished. So it was sensitive to both protease and RNase treatment.

It was extremely difficult to get that work published. Nobody believed it. It was the first example of an enzyme that required an RNA for its activity. It took us about two years to get it published. Various journals just rejected it out of hand or made difficulties. It finally appeared in *PNAS* [*Proceedings of the National Academy of Sciences*]. One of my senior colleagues here agreed to have it refereed and to send it to *PNAS*.

In 1983, Cecilia Guerrier-Takada was working with me as a postdoctoral fellow. She is an excellent researcher. Back then, she was doing some assays of RNase P activity under various conditions, as suggested to us by results of K. Gardiner in N. Pace's lab. She found that in the presence of a high magnesium ion concentration, around 60 millimolar, the RNA subunit alone, which by then we had succeeded in separating from the protein, was capable of carrying out the enzymatic reaction on tRNA precursor substrates. These were reactions that the protein, by itself, could not carry out. If we added the protein to the reaction, it increased the turnover number.

That's a brief history of the discovery. By then (1983), Tom Cech had already published his results on a separate system in which he had shown that RNA was catalytic and so there was much less resistance to our findings. The chemical difference between our system and Cech's system is the following. RNase P is a true enzyme: Cech's RNA is a self-cleaver: it cleaves itself in two places and then it puts two of the three products back together. It splices. In this sense, it is not a true enzyme because a true enzyme is unaffected by the reaction it carries out. Since then, Cech has shown that under various conditions in the test tube he can make his RNA act like a true enzyme.

Did you meet Thomas Cech when you were in Colorado?

No. When I was in Colorado, there was no molecular biology on the campus in Boulder. I got my Ph.D. in the Biophysics Department at the Medical School in Denver. I lived in Boulder for a while and took courses there before I started my research in Denver. Cech didn't arrive in Boulder until about 10 years after I'd left. He is several years younger than I am.

I had originally studied physics and I was in Colorado in the summer of 1962 to attend a summer institute in theoretical physics. I met George Gamow there. He was a very famous and flamboyant physicist. He contributed an important idea also to notions about how the genetic code worked, in the early 1950s. His suggestions turned out to be wrong but they pointed people down the right path. I met him at a party for students and he told me that there was interesting work in molecular biology in the Medical School. I had a superficial knowledge of what was happening. I knew about DNA. I decided to look up some people at the Medical School so I went down there and I met Leonard Lerman and thought that he was doing extremely interesting things. He was studying the physicochemical basis of intercalation, how acridines intercalated in DNA, and similar questions. So I transferred to his department.

I was trained as a physicist and I knew very little chemistry and no biology. This is why my department insisted that I spend a year in Boulder learning biochemistry and, especially, organic chemistry.

You started in physics, ended up in biology, and picked up a Nobel Prize in Chemistry along the way.

Supposedly we uncovered something new about catalysis. I don't think though that this is so. If you look for a proper definition of a catalyst (or an enzyme), you won't see its chemical nature defined in any way. A catalyst is something that accelerates a reaction, but it is not defined as RNA, DNA, protein, or something else. Any large molecule, or even a small one with the right kind of properties, can be a catalyst. From a chemist's point of view, our observation was not something fundamentally new, but it had many important implications for biochemists or biologists. One of my senior colleagues here told me, half-jokingly, "Whatever it is, chemistry or not, it is still great."

Having grown up wanting to become a physicist, I'd read a lot about the history of 20th-century physics. I thought that to be in a place like Copenhagen in the 1920s and 1930s must have been amazing. I regarded the MCR Lab in Cambridge in the same way because in my field at that time it was the preeminent lab in the world. It seemed as if major discoveries were being made there every few months. I was overjoyed to have the opportunity to go there. I knew it would be a great experience. What was great about it was that there were about a dozen absolutely amazing scientists there, several of whom had already won the Nobel Prize. They set the tone for how the place worked.

Were there seminars?

There weren't that many seminars.

Some of the individuals I alluded to included Perutz, who was the head of the Laboratory, Brenner, Crick, Sanger, César Milstein, Hugh Huxley, and Aaron Klug. Kendrew wasn't around very much by then. But the others were working every day in the lab, alongside everybody else. Fred Sanger was a great ultimate example. He himself was working on DNA sequencing and he only had one or two people working with him on the project. He was there synthesizing compounds himself.

Everybody went to tea, according to the English custom, mid-morning and mid-afternoon. These "gods" of molecular biology were there, sitting with everyone at tea. They encouraged everybody to participate freely in discussion and they treated everybody equally. You could be the youngest graduate student or a technician, it didn't matter. They took your ideas seriously. They were also honest and very forthright in their criticism.

You had to develop yourself in two ways. On the one hand, you had to train yourself not to say anything that was superfluous or stupid. The "gods" made it very clear if they felt that you were frivolous or you were thinking in a less than coherent way. One could become very discouraged very quickly if that happened. Some people succumbed. On the other hand, if you were able to engage in the discussions, take advice, and approach the gods only when you had really something to say, it was fantastic. They made you feel part of the enterprise.

Crick and Brenner shared an office, which was highly unusual. They were generating new ideas all the time and found it important to bounce

their thoughts off each other. Their door was always open to others. There was a sign on it saying something like "If this door is closed, just knock and walk in if you are member of the Lab. If you are not member of the Lab, please speak to one of the secretaries first." But the door was open 95 percent of the time. The same was true with all the senior scientists. The most important thing for a young scientist was learning to engage in discussions with anyone and to be aware that once you were engaged in a discussion, you had to be rigorous in your thinking and had to be able to accept criticism without taking it personally.

Do you practice this accessibility here?

I'd tried to run my lab exactly the way the Lab in Cambridge was run and also to treat my students the way my previous mentors, Lerman in Colorado and Meselson at Harvard, treated me.

There had been this long-standing question about the relative importance of proteins and nucleic acids until you decided it in favor of the nucleic acids.

When we found the catalytic properties of RNA, we were working as straightforward enzymologists. Much of the justification for my work was to understand how tRNA works inside the cell and how it is made. We still don't fully understand the details of the catalytic act. However, I was quite surprised by the interest in our work of people who are trying to understand the origin of life. That's where the question of the relative importance or primacy of nucleic acids and proteins comes in.

There was an obstacle in our thinking about the origin of life. One of the essential properties of living organisms is that they transmit their genetic information with some degree of faithfulness. How was this done in the first organisms? The idea was that first you had to have an information-bearing molecule, something like DNA or RNA that would code for protein. But if you start with DNA (or RNA), how were you going to replicate it unless you had proteins present? All the enzymes we knew about at that time (about 1982–83) that copied DNA or RNA, or DNA into RNA, were proteins. All these "polymerases" are protein enzymes. Restated, you want DNA or RNA because they code for proteins. On the other hand, you can't replicate DNA or RNA without proteins. So how do you get the whole cycle started? That was the problem. When the catalytic properties

of RNAs were discovered, that obstacle was removed because we generalize very quickly. For example, I found a hydrolysis reaction carried out by RNA. Cech found a similar reaction, although his works by a transesterification reaction. He also found a ligation reaction, a joining reaction. So we knew three reactions that were carried out by RNA. Immediately, many people said that if RNA intrinsically can be a catalyst, and chemically there is no reason why it should not be, then that means that RNA can carry out any chemical reaction.

Thus, the general statement was made, "RNA can be a catalyst." If that is the case, you don't have to have proteins to get the whole process of life started. The next step, that Walter Gilbert and others made, was the statement that you don't even need DNA to get life started because RNA encodes the information in the same way as DNA and, if it's a catalyst, it can do everything. Gilbert named this scenario "the RNA world."

Many people think now that life started in the RNA world. There are some difficulties with that because of the chemical composition and properties of the primitive ocean and atmosphere: it is not clear that RNA would be stable under these conditions. Thus, some adjustment will be needed in our thinking. That's what is meant by the primacy of nucleic acids. This was the big issue that the press covered. They had much less understanding of the enzymological problems and the chemistry involved, so they just ignored them and focused on the origin-of-life question.

It's now almost 10 years since you received the Nobel Prize. How did it change your life?

I was 50 when I received the Prize, much too young to retire. I had just served four years as Dean of Yale College and was ready to get back to the lab. I never intended to become an administrator in the first place. My life did change in some ways. After the Prize, we all relaxed for about eight months. Then it was time to get back to work, and I put a lot of pressure on myself, and the people around me, to sustain a high quality of research. I think now that I put too much pressure on everyone. I also responded to a lot of lecture invitations, but then gradually I decided to restrict the number of lectures I was willing to give. For a few years my life was pretty strenuous, and I'm trying to keep these engagements to a minimum.

What is your current research interest?

We're still working hard on understanding the molecular details of the reactions catalyzed by RNase P. Mainly, we work with RNase P from *E. coli* because it's easy to study. We have also been studying RNase P from human cells and from baker's yeast. The latter are somewhat more complicated enzymes. That takes up about two thirds of my lab work. The other third is concerned with some practical applications that came out of our work on RNase P, that is, out of our basic research. We had been working on the properties of the enzyme for about 20 years when we found something that could be of practical use. I'm also advising a couple of companies. We have a patent on a process that uses RNase P to turn genes off at will. This one company licenses this patent from Yale.

Some years ago you gave a series of public lectures. The title, "Understanding Life in the Laboratory," was meant in what sense?

It was meant to have a double meaning. I have been encouraged to put these 10 lectures into a book but I haven't done it yet. By "life" I mean both the process of pursuing a research goal in the lab and the social aspects of the professional world of science.

Are you a rather private person?

I'm not interested in spending my time to make myself well known or to become very active in organizations that are engaged in the politics of science. I don't get much satisfaction from that. There are many more important things to do.

According to some, your discovery of the catalytic potential of RNA was one of the two most important discoveries in biology in the past half a century, the other being the double helix of DNA.

That's just one person's opinion.

You resolved the primacy dilemma.

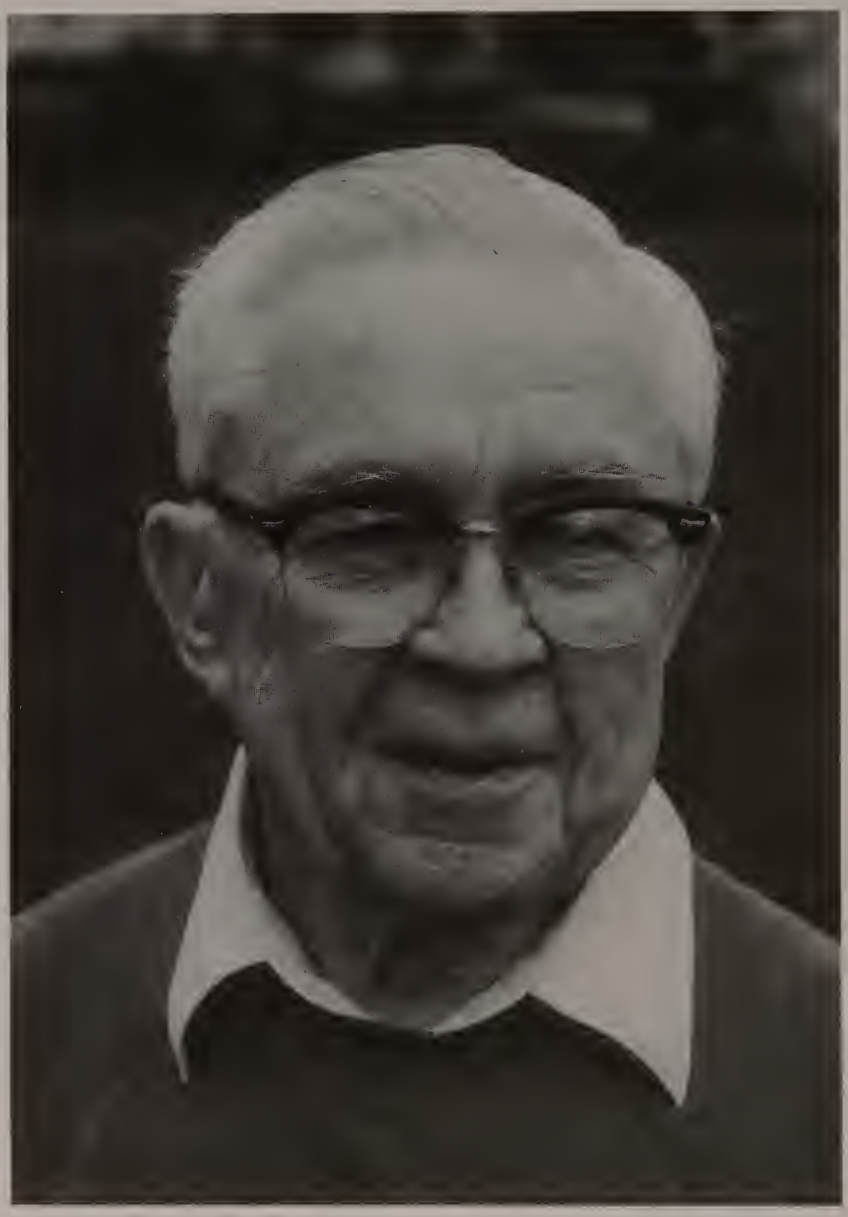
As with all things, it's a temporary answer.

Isn't everything in science temporary in a way?

We are always building on previous work. However, I do regard the laws of physics as rather permanent.

Of course, I understand that originally you didn't set out to solve the primacy problem.

Absolutely not, and I still take all these discussions with a grain of salt because it's impossible to do conclusive experiments on the origin of life.



Edward B. Lewis, 1997 (photography by I. Hargittai).

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Edward B. Lewis

Edward B. Lewis (b. 1918) is Thomas Hunt Morgan Professor Emeritus of Biology (Active) at the California Institute of Technology. He obtained a B.A. in biostatistics from the University of Minnesota (1939) and a Ph.D. in Genetics (1942) and an M.S. in Meteorology (1943), both from the California Institute of Technology. He was co-recipient of the Nobel Prize in Physiology or Medicine in 1995 "for discoveries concerning the genetic control of early embryonic development." He is a Member of the National Academy of Sciences of the United States and a Foreign Member of the Royal Society (London), among other memberships. His many distinctions include the Wolf Prize in Medicine (Israel, 1989) and the National Medal of Science, which he was awarded in 1990. Our conversation was recorded on February 15, 1997, in Pasadena, California, and the text was finalized by correspondence during the spring of 1998.*

You came to Caltech in 1939. What is the main difference between the Caltech of 1939 and 1997?

It was a relaxed and unhurried atmosphere in 1939. The Biology Division received financial support from the Rockefeller Foundation as well as Institute funds, and some support for research positions from the Carnegie Institution of Washington. As a result, the faculty didn't have to write grants. Research

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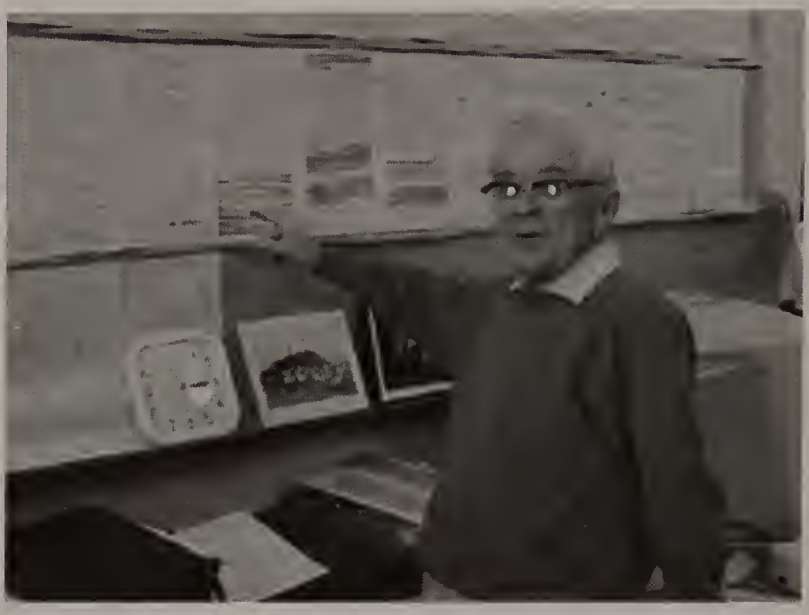

Edward Lewis pointing at the *Drosophila* gene map in his office, 1999 (photograph by Magdolna Hargittai).

Edward Lewis and Seymour Benzer at Caltech, 1999 (photograph by I. Hargittai).

groups tended to be much smaller than now, and faculty members could give more individual attention to their graduate students.

Did you interact with Linus Pauling?

I mainly got acquainted with him during the "fallout" period. This was the time when the Atomic Energy Commission was conducting tests of atomic devices in Nevada. Being above ground, these tests released radioactive fallout over much of the continental U.S. One day, while having lunch at our faculty club with some of our physicists, the question came up whether there could be any danger from such fallout. I decided to look into the matter and spent several hectic months doing so. I found out as much as I could about what had happened to Japanese A-bomb survivors. I studied published studies by others of adults treated with X-rays for ankylosing spondylitis, and of infants treated with X-rays for enlarged thymuses; in addition, I collected data on radiologists. Every group experienced a significantly elevated risk of leukemia. What was new was that all of the studies were consistent with a risk of one to two cases of leukemia per million persons per year per rad unit of radiation. No one had put all of the data together before. I published it in *Science* in May 1957 [*125*, 965–972].

I cited a famous paper published in *Science* in 1928 by H. J. Muller. The paper is an account of his discovery that X-rays can induce mutations in the germ cells of *Drosophila* — a discovery for which he was awarded the Nobel Prize in Physiology or Medicine in 1946. The paper contains a very prophetic remark that X-rays could also produce cancers by inducing mutations in somatic or body cells as opposed to mutations in germ cells. So logically you might expect that fallout could result in cancers if they result from somatic mutations and if there is no threshold dose of radiation for their induction. Since it had become clear by 1957 that there was no good evidence for a threshold dose below which no germ cell mutations would be induced, it was reasonable that there would not be one for somatic mutations either.

To get back to your question, I showed an early draft of the paper to Linus, who popularized the risk estimates I had calculated in his campaign to stop the testing of atomic weapons. He multiplied the risk estimates by rather a larger number of persons than would actually have been exposed to the estimated doses from fallout. You will remember that it was his campaign to stop testing that won him the Nobel Peace Prize in 1962.

The 1957 paper came out in May and that was a time when the Joint Committee on Atomic Energy of the U.S. Congress was holding hearings. I did not know that but the paper was well timed. I was invited to testify and gave estimates of how many leukemia cases might be produced in the U.S. from then known fallout levels, based upon my estimate of the risk per rad.

I might add that I later published a more detailed study of radiologists certified by the American Board of Radiology, and with the aid of a small grant from the American Cancer Society, I obtained, and analyzed 425 death certificates of radiologists dying between the ages of 35 to 74 during the years 1948 to 1961 [*Science* **1963**, *142*, 1492–1494]. I found a way of checking on whether the higher than expected number of deaths from leukemia might be owing to better diagnosis of the disease in this group of medical specialists. Court, Brown, and Doll in their study of irradiated arthritic patients had shown that one form of leukemia, chronic lymphocytic, appeared not to be increased in such patients, even though it is one of the commonest forms of leukemia in older age groups. In my American radiologists study, there were 12 recorded leukemia deaths, among which there was only one death from lymphocytic leukemia, and that from the acute rather chronic form. This method provides a kind of built-in control for assessing leukemia risks from ionizing radiation and has since been used successively in a number of studies by others. I also discovered that this group of radiologists suffered a significant increase in multiple myeloma. This was the first report of such an association. Since multiple myeloma is essentially a leukemia of the plasma, or antibody-producing cells, I was puzzled why it had not shown up in other groups, especially the well-studied group of arthritic patients that I have already referred to. I finally realized that that group and others were still relatively young compared to the radiologists I had been studying. More recently, when Doll and his group followed their ankylosing spondylitis patients for an additional 34 years [Weiss, H. A.; Darby, S. C.; Doll, R. *Int. J. Cancer* **1994**, *59*, 327–338] they found a significant increase in deaths from multiple myeloma.

Should the women who were exposed to radiation around Chernobyl have second thoughts about having children?

I doubt that persons other than workers in the immediate vicinity of the reactors would have received doses large enough to produce a significant increase in any genetic defects. Even careful studies of the A-bomb survivors

in Japan have failed to show clear evidence of an increased risk of genetic defects. The reason is that it is hard to detect new mutations, since all of us tend to carry hidden deleterious mutations that have been handed down from previous generations. My guess is that the main concern from the Chernobyl accident is the risk of thyroid tumors from the release of radioiodines, and the group most likely to be affected will be individuals who were infants at the time of the accident and who may have been drinking fresh cow's milk that would likely have been contaminated with radioiodine.

I had been shocked, but not surprised, to find that the Atomic Energy Commission (AEC) had totally failed to understand the special hazard to infants and, for that matter, fetuses from radioiodine (^{131}I), which is one of the main constituents of fallout. Two things were overlooked. First, the thyroid of an infant weighs only one gram or less compared to about 20 grams in the adult. The ^{131}I beta particles are so short-ranged in tissue that all of their energy is deposited within even the small thyroid of the infant. The result is that the infant gets roughly 20 times the dose that adults get for the same uptake of radioiodine in the thyroid. Second, cows feeding on pasture contaminated with ^{131}I, as happened in the case of some Nevada tests, concentrate the isotope in their milk; the result was that infants who consumed fresh milk would ingest much more ^{131}I than they would from any other source, such as inhalation. I calculated that the average infant in the U.S. received a thyroid dose from ^{131}I equal to about 0.1 rad per year and that the range of doses that would be expected to occur might be 10 times less or 10 times more in some infants depending upon many variables such as the actual amount of fresh milk consumed and variations in geographical deposition of the isotope. Yet the AEC had been assuring the public that fallout doses would be far below 0.1 rad per year.

In this lab there are bottles full of fruit flies everywhere. I know that related research had been done before you joined in. Would you care to give an overview of this research in historical perspective before we move on to your contribution?

Thomas Hunt Morgan, who founded this Biology Division in 1928, won the Nobel Prize in Physiology or Medicine for his studies of these *Drosophila* flies. Commencing in 1910 at Columbia University, he and his students were able to use these flies to discover many new laws of genetics. It all began in 1910 when he discovered a white-eyed fly — the normal flies

have red eyes. Morgan showed that this mutation followed a new law of sex-linked inheritance. For the first time, Morgan's discovery explained how color blindness and hemophilia are inherited in people. Morgan and his three students A. H. Sturtevant, C. B. Bridges, and H. J. Muller went on to make a succession of brilliant discoveries — Sturtevant has described them in his book, *A History of Genetics*, published by Harper and Rowe, New York, in 1965.

How would you summarize your main contribution to genetics?

I think it was to show that genes could be used to study how an animal develops a head, thorax, and abdomen. Yet, as is often the case, I had no intention of trying to study how this could happen. Instead, I was hoping to find out how new genes arise from old genes. The hypothesis is that new genes arise by a two-step process. First a gene becomes duplicated in tandem. If we represent a gene by the letter A, then such a duplication can be written as AA. Sturtevant had actually studied a famous bar-eyed mutation in Drosophila that turned out to be just such a duplication event. The second step in the hypothesis that can lead to a new gene is to have one of the duplicates mutate and carry out a new function, leaving the old gene to carry out the old function. I searched for cases that might be such duplications. (Bridges had predicted that certain double-banded structures in the normal salivary gland chromosomes were just such duplications). It is necessary to think about it in symbols. In symbols we can write that AA has become AB, where B is the new gene and A the old gene. I found a case that nicely fitted the hypothesis and that involved some striking eye mutations known as star and a second mutation I called asteroid. Although acting like a single genetic unit, they turned out to be separable by crossing over, the orderly process of recombination between the maternal and paternal chromosomes — again a process discovered by Morgan. That was my doctoral thesis. It is still not known exactly what these mutations are at the molecular level.

What was the advantage of working with the flies?

There are many advantages. Large numbers can be reared inexpensively in a confined space. At room temperature, the generation time is only 10 days. A single pair can produce hundreds of offspring. A wealth of mutations were available and, thanks to Bridges, were already kept in pure breeding stocks at the Caltech *Drosophila* Stock Center. It is relatively easy

to detect mutations in the first generation following irradiation of the parents. Another amazing feature is that the chromosomes of the salivary glands of these flies are a thousand times larger than chromosomes in our cells.

Why are the chromosomes so large?

The salivary gland cells secrete a lot of a protein glue that the larva uses to attach the pupal case to the substrate. Apparently, it is easier to make extra copies of all of the genes in order to make many copies of the genes that make the glue. The chromosomes are giant because they undergo repeated divisions and yet the cells don't divide. After 10 divisions, each cell ends up with 1024 chromosomes that form a tightly packed bundle. We dissect out the salivary glands of the larva and squash them in a DNA stain and study the banding pattern. Using deficiencies and duplications for genes, we can actually locate the specific bands that contain the genes we are interested in.

When did you carry out the research that led to the Nobel Prize?

It started in 1946. I wanted to see if I could find more cases of gene duplications that had created new genes. I worked on several cases, but the one that turned out to be most interesting was a group of so-called bithorax mutations, the first one of which was found by Bridges in 1915. They are known as homeotic mutations since they change one structure or organ into a homologous one. Bridges's mutation caused the fly to begin to develop a rudimentary extra pair of wings on its thorax. Actually, the third segment of the thorax is being converted into the homologous second segment. Much later, by the way, we found that by combining three different mutations occupying three different loci we obtained a fly with two pairs of wings instead of one. Bridges had saved and put in the stock collection at Caltech all of the known mutations of this type. By 1950, I had found that they occupied three loci instead of one as had been assumed — locus is what we call the site in the chromosome that a gene occupies. By 1978, I had been able to induce a sufficient number of new mutations with X-rays to identify nine loci. Amazingly, the loci are colinear, meaning they are in the same order in the chromosome as the order in which the genetic elements at those loci are expressed along the body axis of the fly. It became clear that the bithorax complex, as we call this group of loci, programs the development of not only part of the thorax but the abdomen as well. I speculated that the bithorax

genes were switching certain genes off, thereby allowing others to turn on and make the body organs.

Was it chemistry that finally confirmed it?

Yes, recombinant DNA chemistry carried out by others showed that I had been studying a special class of genes that make proteins that bind to DNA and are called transcription factors. The bithorax complex was, I believe, the first case that implicated such factors in controlling the development of higher animals. Fortunately, the duplication hypothesis was in the back of the minds of Walter Gehring and his group in Basel, Switzerland, and Matthew Scott, now at Stanford University. Independently, they discovered that Ultrabithorax, one of the bithorax genes, and Antennapedia, a gene that is involved in transforming more anterior regions of the fly, each contain a highly conserved sequence of 180 DNA base pairs. It was soon found that two other genes of the bithorax complex also carry this sequence, which Gehring named the homeobox (HOX), and so do other genes that belong to another complex that Tom Kaufman had identified and named the Antennapedia complex. Gehring's group soon found that the HOX sequence is highly conserved in vertebrates as well as *Drosophila* and that in vertebrates the complex is not split into two as in *Drosophila* but is still one intact cluster. So finding that HOX genes in the fly are remarkably like the HOX genes of vertebrates was truly amazing. Also they are arranged in the same colinear manner as first found in the fly. One difference is that in vertebrates starting with the fish there are four sets of the HOX complex, each in a different chromosome. Not all of the genetic elements in the bithorax complex code for proteins; one at least codes for an RNA that does not make a protein and therefore is still a gene in a biochemical sense. This is a new exciting area of molecular genetics in which immense regions of DNA not coding for protein are very important in telling the transcription factors where and when to function in development.

So the molecular work by others really provided nice justification for the tandem gene duplication hypothesis for the origin of new genes.

Avery, MacLeod, and McCarty should have received the Nobel Prize for determining that DNA was the substance of heredity.

I am not well enough informed to comment on this. I know that Watson has said that he and Crick were not convinced that DNA was the hereditary

material until the late Al Hershey — who shared the Nobel Prize in Physiology or Medicine with Delbrück and Luria — showed that when bacteriophages infect a bacterium it is the DNA and not the protein which is transmitted.

Genetics is so important and yet outside the sciences we hear very little about genetics.

It is a 20th-century subject whose importance for the study of biology has been slow to be recognized even until very recently. Until the one-gene-one-enzyme concept was demonstrated by Beadle and his collaborators, biochemists had no idea how enzymes were produced. Even then, progress was set back because it was thought that genes were proteins containing prosthetic groups composed of DNA. Also, there were some who felt that genetics could not explain how development of an animal takes place. Instead, they hoped that self-replicating cytoplasmic particles would explain development. Another reason was that textbooks not only of biology but of biochemistry and of medicine made little or no mention of genetics, and if they did, it was only to explain the laws of inheritance and not the role that genes might play in controlling almost all biological processes. At first it wasn't clear that what was learned by studying organisms like *Drosophila*, bacteria, and fungi applied to people. Now we know that many of the genes of the fly are present in us where they often function in

George Beadle, Alfred Sturtevant, and Edward Lewis around 1960 (photograph courtesy of the Archives, California Institute of Technology).

much the same way — examples are the HOX genes of the flies, which as I have been saying, also are in people, where they seem to determine the body plan in much the same way that they do in flies.

How did you start out?

I was born in 1918 in Wilkes-Barre, Pennsylvania. My parents were very supportive of my interest in animals. I went to the public library and read books to learn how to build aquariums and terraria. I also read books by Bertrand Russell and enjoyed his then radical views about science, education, religion, and human affairs in general. But what really started me was a book by H. S. Jennings titled *The Biological Basis of Human Nature*. It had simple diagrams that explained the Morgan's law of sex-linked inheritance. The library also subscribed to the journal *Science*. In one of the issues, I saw an advertisement for cultures of *Drosophila* that could be ordered from a Professor Rifenburgh at Purdue University for $1.00 each. A high school friend of mine, Edward Novitski — now a retired professor of biology at the University of Oregon — and I ordered cultures and began growing *Drosophila* in our high school biology laboratory. Our biology teacher, who was also the athletic coach, generously let us use the lab after hours for our experiments. We were soon helped by Bridges who, in correspondence with Novitski, showed us how to proceed and sent us more mutant strains — free of charge!

I went to Bucknell College in Pennsylvania for one year after high school on a music scholarship. I transferred to the University of Minnesota for undergraduate work and after two years received a bachelor's degree in biostatistics. Then I came here to Caltech in 1939. In three years I received my Ph.D., which was typical in those times. From 1943 to the end of World War II in 1945, I was a meteorologist with the U.S. Army Air Force in the Pacific theater. Upon returning, I joined the Caltech faculty as an instructor. I began the research on the bithorax complex at that time.

Vinca minor *has often four or five petals, and very often all the petals turn in one direction. So the flower has rotational symmetry only. No symmetry planes. There is no reason, though, for this flower not to have planes of reflection. A botanist told me this is probably a result of mutation.*

Presumably, genes evolved that accomplished this because it gave the plant some selective advantage. A mutation in such genes should abolish this symmetry, but I do not know whether such mutations are known.

What do you think of genetic engineering?

It's wonderful.

It could be misused.

It could be. But there are bound to be great benefits of genetic engineering, especially in diagnosing diseases and developing cures. Vigilance will be needed to be sure that genetic engineering is not abused.

Not only have scientific discoveries been abused in the past, scientists themselves have often been persecuted for their beliefs. A tragic chapter in recent times was the persecution of geneticists in the Soviet Union during the Stalin era by Lysenko and his followers. Lysenko claimed that heredity was not controlled by genes and chromosomes but by the environment. He gained power because such a view supported Marxism-Leninism, which denied that there could be a genetic as well as an environmental component to human behavior. Lysenko's claims could not be substantiated, but meanwhile geneticists in the Soviet Union were persecuted, ridiculed as "Morgan-Mendelists," and prevented from teaching genetics or doing research in it. Such persecution of a science is a warning to the whole scientific community that it can happen even in modern times. I find it alarming that there seems to be a movement on to attack the whole idea of genetic engineering.

Can genetic engineering make a better human being?

This question is too loaded with ethical and other implications that I would rather not discuss.

Could genetics data about intelligence be useful?

Yes, but we need much more information about the genes involved. Anything as complex as intelligence will be determined by a multitude of genes interacting with one another. It is well known that persons who have an extra 21st chromosome have Down's disease and are quite handicapped both mentally and physically. What does this tell us about genes involved in intelligence? It tells us a lot. First, the 21st chromosome although very small, still has many hundreds of genes. Three sets of these genes, even though none of the genes need be defective, is sufficient to disrupt virtually every organ system of the body, and the brain is no exception. Fortunately, for most of the larger chromosomes the effects of an extra chromosome

are so drastic that the individual dies before birth. In another example, persons who have an abnormal number of sex chromosomes are at risk of mental problems. Females have two X chromosomes and males an X and a Y chromosome. Persons who are XXY are not only intersexual they tend to be of lower intelligence. Males with two Y chromosomes instead of one also are at higher risk of having mental problems, including in some cases an overly aggressive behavior.

Single gene defects have been identified in flies that have effects on the fly's behavior, or memory, or ability to learn. Using DNA from such genes, the homologous genes have in some cases been already identified in human beings. This is a start toward learning what such genes do in people.

Pedigree and twin studies of intelligence in people have shown that many genes must be involved in producing the wide range of intelligence exhibited in the general population that are genetically based — of course, cultural or other environmental influences play a big factor too but are not exclusively involved by any means.

If you mean can we expect to use genetics to improve intelligence, that is really science fiction. Literally thousands of genes are involved in

Edward Lewis playing his flute in his office, 1999 (photograph by I. Hargittai).

determining how the brain functions. Above or below average intelligence then follows the same rules that govern other complex traits such as human stature or yields of corn, for example. It is the aggregate of many genes, each with a relatively tiny effect on brain function that determines whether a person's genetic endowment will confer above or below normal intelligence.

How about chirality?

I don't know what the actual mechanism is. There seem to be several genes that are involved in determining handedness. Also the brain hemispheres differ in dominance — some people have the left side dominant, in others it is the right side.

Do you have children?

We have two boys living. A third boy died in a mountaineering accident when he was 15 years old. Our older son is a lawyer, and the younger one a biology technician.

Your wife?

She is very artistic. She could also have been a great scientist — she found one of the most important mutations affecting development known, called Polycomb, which is now attracting much research in many labs. She chose instead to paint and rear our children.

You look very young.

I try not to get overweight and, starting at age 60, I took up exercising to keep fit.

What keeps you going so well?

I try to swim every day, and if not, jog. Also I am in a state of constant excitement about the problems I am working on. There are a lot of unexplained genetic phenomena that are most easily tackled by studying *Drosophila*. So I keep busy in the lab.

Rita Levi-Montalcini, 2000 (photograph by Magdolna Hargittai).

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Rita Levi-Montalcini

Rita Levi-Montalcini (b. 1909 in Turin, Italy) is Director Emeritus of the Institute of Cell Biology of the Italian National Council of Research (CNR) in Rome. She shared the Nobel Prize in Physiology or Medicine for 1986 with Stanley Cohen (b. 1922) of Vanderbilt University School of Medicine, Nashville, Tennessee, "for their discoveries of growth factors." When I visited her in June 2000,* she was 91 and still very active. We had two meetings, one at her Institute and the other at her home. She continues her research although she is no longer involved in laboratory work because of her deteriorating vision. Her and her co-workers' latest discovery is the important role of the nerve growth factor (NGF) in diseases that have to do with allergy. She received her latest honorary degree, from The Hebrew University of Jerusalem, for this new development. Eight people are working currently in her group and they have ongoing collaboration with others in Canada, England, Poland, and the United States with further interactions in Israel and Sweden.

Rita Levi-Montalcini came from a professional family, but her father was reluctant to support her going to medical school. Finally, he relented and she graduated a M.D. from the University of Turin. However, the so-called Jewish laws of fascist Italy prevented her from practicing medicine. Being barred from academic employment she set up a home laboratory and started her experiments in neuroembryology with chicks. During her university years she was a student of a famous histologist

*These are excerpts from an interview prepared by Magdolna Hargittai.

Giuseppe Levi (1873–1965) who was also mentor to two other future Nobel laureates, Salvador Luria (1912–1991, Nobel Prize in Physiology or Medicine, 1969) and Renato Dulbecco (b. 1914, Nobel Prize in Physiology or Medicine, 1975). In Levi-Montalcini's experiments at her home laboratory she was influenced by Viktor Hamburger's (b. 1900) research at Washington University in St. Louis, Missouri. After the war, Hamburger invited Levi-Montalcini to join him in St. Louis where she stayed for nine years. In the middle of her stay she made a crucial study-trip to Rio de Janeiro to work with Hertha Meyer, a former assistant of Emil Fischer. There she performed some experiments and recognized what later became known as the nerve growth factor. At the time of her return to Hamburger's laboratory in St. Louis, Stanley Cohen joined them and a period of exceptionally fruitful collaboration followed. In addition to Levi-Montalcini's discovery of NGF, Cohen discovered the epidermal growth factor (EGF).

According to the presenter at the Nobel Prize ceremony, "Rita Levi-Montalcini showed, in a series of brilliantly performed studies that NGF is not only necessary for the survival of certain nerves but also regulates the directional growth of the nerve fibers. The nerve cells die when NGF is blocked by antibodies. NGF is produced by the target cells which lure the nerve fibers to grow in the direction. Injections of NGF into the brain cause the outgrowth of specific nerve fibers. This neurotropic effect on NGF offers an explanation of how nerve fibers find their way through the tangle of nerves in the brain." [Hall, K., in *Nobel Lectures: Physiology or Medicine 1981–1990.* Editor-in-Charge T. Frängsmyr, Editor J. Lindsten. World Scientific, Singapore, 1993, p. 328.]

Shortly after her Nobel Prize, Rita Levi-Montalcini wrote a beautiful autobiographical account *In Praise of Imperfection* [Basic Books, Inc., Publishers, New York, 1988; translation by Luigi Attardi from the original Italian *Elogio dell'imperfezione.*]

I've read your book In Praise of Imperfection ...

Unfortunately, all my other books are in Italian, neither of them was translated into English, but some Spanish and French translations have appeared.

The last one, to come out soon, is a selection of letters I wrote to my mother about my work at the time I made the discovery, that is half a century ago, when I lived in the United States. It is a day by day sequence of letters. Its title is *Cantico di una vita,* something like *The Hymn of Life.*

The letters show that I was full of enthusiasm. We have just recently found about fifteen hundred letters in a wooden crate in the basement of our house — I thought they were lost. I selected about 200 of them, and edited them into this book; perhaps the best book I have ever written. The letters are all long and neat letters, some of them are 8 pages long and no one word is crossed out or changed in them.

Now I am working on another book. There is a beautiful, almost biblical poem by Yeats, *The Second Coming*, but it is very pessimistic about the future. I am not like him; I have a basically optimistic attitude, so the title of the book I am writing now is *The New Coming*. It is about the possibility of saving the human species (and other species) by changing the relationship to children, to women, and to young people. This is the only hope to survive.

Perhaps the most interesting book I have written, and it is in English, *The Saga of the Nerve Growth Factor*, it is a collection of all the papers and articles that have appeared on this topic and some of which are no longer available.

It is beautiful that you have the energy to work on all these books.

It is no problem. I have excellent help; four people help me. My vision is very bad, I have problems with reading and writing but it is not as bad as you imagine because I can still think.

What turned you to science?

Oh, I believe I have never become a scientist. I am more of an artist. I just use the nervous system as the area of my study. My approach to science is this: you can do it! I was a student of Guiseppe Levi, an outstanding Italian scientist. Three Italians have got the Nobel Prize, Luria in 1969, Dulbecco in 1975, and myself in 1986. All three of us have become scientists just because we were students of Guiseppe Levi. He himself never received the Nobel Prize.

But I don't believe that I have ever been a scientist. My twin sister is an artist, a painter, one of the best in Italy. My brother was an architect, and an excellent sculptor. I believe that my approach to science was from the point of view of the beauty of the nervous system and not just plainly because I was interested. Still now, I don't believe I am a scientist, I approach science more from an artistic point of view than from a scientific

one. Ever since I entered into the field of science as a young person, I have never thought that I would become a scientist. I was more interested in social problems than in science. It was just my good luck that I was prevented from continuing my work as a medical doctor. Thus I had to work in my bedroom in a little laboratory and that is where I did the first steps of the work that later led me to Stockholm.

My interest in science was just casual and I owe it to Benito Mussolini who prevented me to become a regular doctor, because I was not Aryan.

Italy was a much better place than some other countries in Europe as far as anti-Semitism is concerned.

No doubt about it. Much better than Hungary, for example, which was terrible. You have a lot of fantastic scientists. I was a friend of Leo Szilard, for example, and I know that Hungary was a very anti-Semitic country as was Germany or Austria, Poland or Russia. Italy just became that because

Rita Levi-Montalcini among the participants of a meeting on genetic neurology in Chicago, 1949 (courtesy of Rita Levi-Montalcini).

of Mussolini becoming a friend of Hitler. Mussolini's lover was a Jewish lady, Margharita Sarfatti, whom he abandoned later. But Italy has never been an anti-Semitic country. I never considered this as a problem. I was totally indifferent to it. I always had many friends, and even in the period of Mussolini's anti-Semitic laws, all of them remained my friends, even if they were not Jewish. There was not any feeling of anti-Semitism and people did not care about it. My fiends were both Jewish and Catholic; it never made any difference to me.

Leo Szilard was a fantastic person and we liked each other. I mean we just met scientifically, but I think that he was the best person I ever met. His wife came to me one day, I was at the Salk Institute that time, and said: tell me about yourself because my husband talks about you all the time! And I said: I don't know why. He was a man of tremendous stature, scientifically as well as humanly. I was always very close to him. Unfortunately, I did not have the privilege to know him really well. We were together at the Salk Institute, in La Jolla, shortly before he died. But I had a tremendous respect and admiration for him. He was a gigantic person in science, like Fermi. He never cared about popularity, he was always concerned only about real, important issues.

If you look at the most successful scientists, or at Nobel Laureates, you cannot help noticing how many of them are Jewish.

Arthur Kornberg, a very close friend of mine, told me that from City College in New York there were 24 Nobel Laureates and 23 of them were of Jewish extraction. I like to speak of "extraction" because I do not believe in race.

How do you explain this, is it genetic or tradition ...

Tradition — only tradition. Today the Chinese people have become very good. In Jewish families it was the tradition to care for children, and to help them, to direct them to a career of success; I believe that this is still so. It is difficult, of course, to say, where is the borderline between genetic or not genetic, but there is no doubt that Jewish people have this tradition to care for their children and to send them to the best possible schools. Most great scientists are children of very simple people, who escaped from the pogroms of Russia or Poland, and they became Nobel Prize winners.

Don't you think that persecution, in a way, also was a reason — they wanted to excel in spite of all odds.

Yes, the obstacles were useful. Again, it is difficult to draw the line between genetic and environmental effects.

In my own case, I came from a very cultured, very highly educated Jewish family. We were absolutely not observant, my father and mother never went to the Synagogue, they did not care about that. I only became Jewish when the law came against us, before I never knew I was one. I had both Jewish and Catholic friends and it never was a problem. Even after the racial laws, they remained friends. People did not much care about these laws, of course, later many became anti-Semitic because they wanted to make success in life. Now I feel Jewish. But I became Jewish only when the racial laws came, after the persecution, not before.

Did you know Primo Levi?

He was a splendid person, he wrote the best book that will ever be written. I am sure, absolutely sure that he never committed suicide, he may have lost his balance because he was very weak, and perhaps that is why he fell down. The family insisted that it was suicide but I am sure it was not; I knew him too well. He should have been interviewed about that time and he was absolutely far away from even remotely considering of taking his own life.

We were good friends but we did not meet often, he lived in Turin and I was in Rome. I talked with him shortly before he died, I told him, Primo, come to Rome, we could go to the same psychiatrist. It was just after my Nobel Prize and I was upset by too much popularity, which I could not handle well. So I went to see a psychiatrist. But Primo said no, I would never leave my mother, not even for 1 hour — and then he fell down the stairs. It is absolutely out of the question that he killed himself.

Would you care to tell us something about your current interest in research?

The isolation and identification of the nerve growth factor (NGF) about half a century ago was only the beginning of a research, which is now centered on the study of the role of this molecule on homeostatic processes concerning the peripheral and central nervous system as well as immune and endocrine

systems. The recent development of this study opened the possibility of utilizing this molecule for the most diversified pathological disorders of different etiologies.

Could we go back in time and talk a little about your decision, against your father's will, to enter University?

My father came from a very large family of 18 children. One of his sisters became an excellent mathematician; one of the first women to get a degree, another received a degree in literature. My father thought that their marriages were not happy because it was difficult for them to combine family and profession. He had three daughters, my elder sister who just died about two months ago, my twin sister and myself. He decided that since it is so difficult to find the balance between family, children, spouse, and a profession, we should not get a higher education. I was furious, so I decided that I would never marry, I did not want to have children but I wanted to study. So when I was 21 years old, I went to see my father and told him; I don't care about being a wife or a mother, I want to study. He said: Although I am not in favor of this decision, I do not wish to prevent you. My father died in 1932, one year after I entered medical school. Our relationship is best described in the dedication I wrote in my book *In Praise of Imperfection.* It reads: "To Paola and the memory of our father whom she adored while he lived and whom I loved and worshiped after his death."

However, much earlier, when I was still a very young girl, I already decided that I would never marry and have children because that would interfere with my goal of serving people. I never thought of becoming a scientist; I wanted to be engaged in a social profession and that is why I entered medical school.

I was moved by the motto of your book, a Yeats poem, The Choice. *It starts with the following lines:*

> *"The intellect of man is forced to choose,*
> *Perfection of life or of the work"*

Does it have to be an either/or situation?

A beautiful poem, isn't it? Today, yes, it is different. All the women working with me now are married and have children. Although it is also true that

most of them are divorced ... When I was a young person it was not so easy. Of course, even now, it is easier to make one choice and not both. I am very very happy about the choice I made, I have never regretted it, I believe I made the best choice I could have made.

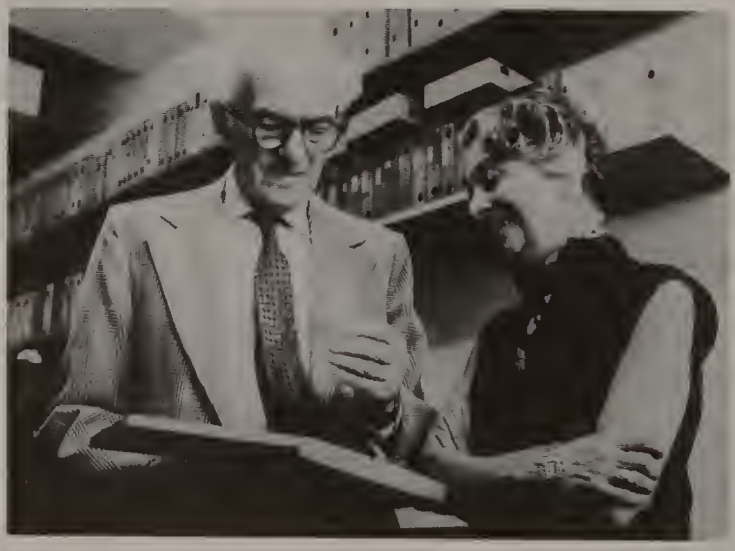
It is interesting that your twin sister made the same choice.

Yes, although she had a much more difficult life. She is very restrained; I am much more open and make contact with people easier. She is an artist but she never cared about being popular among art critics. Now she is recognized as the best Italian woman artist of the century and had tremendous success. Unfortunately, by now she totally lost her interest in everything; she does not have Alzheimer's, but is not interested anymore. She has always been very close to me and we live together.

You have spent a long time at Washington University in St. Louis. What was the atmosphere there?

It was excellent. Very cordial, very generous and we all had a very cordial relationship. Viktor Hamburger will be a hundred years old this coming Sunday, on July 9. I don't think that I will go and see him, but we always had an excellent relationship.

At the time you went there, Washington University was an excellent school, many great scientists worked there, like Hamburger, the Coris,



Rita Levi-Montalcini with Viktor Hamburger in 1970 (courtesy of Rita Levi-Montalcini).

Kornberg, and so on. Nowadays it does not have such a big name anymore. What makes a school to stand out at one time and than loose its momentum?

I believe that it still is a very good school. But I think it just depends on the people. It happens that one person of excellence goes there and attracts other people but when that person moves the others also go. In the U.S. it is so easy to move. Anybody might be called by a better university, being offered better conditions and then people move. I myself was called by many universities but I never decided to go.

Who are your heroes?

Primo Levi. And Leo Szilard, as I mentioned before. Also all people, who made the best of their lives, such as my sister, Paola. Of course, she is not my hero, she is simply the person I love and admire most. I also have very good contact with many people. For me it is very easy to get into excellent relationships with people. It is probably just my character; I am open and optimistic.

But as a first, I think it is Primo Levi; from the point of view of his capacity. His literary works are marvelous. But, as I said, Leo Szilard also, from the scientific viewpoint.

Whom do you consider your best pupil?

Perhaps Luigi Aloe. He is more to me than just a pupil, he has worked with me for over 30 years. It is difficult to say, I never considered myself a teacher. I just lived in a very simple way, contacted young people, and never thought of being a master in any way. My life is very simple. I never considered to be anything at all. There is the book coming out, that I mentioned before, *Cantico di una vita*. I only speak of the positive side of my life, I never mention the negative. I never mention the difficult moments I went through, never, only the positive ones. So in a way I never wanted my mother and my teacher, Guiseppe Levi, to know that I had difficult moments, just the good things, the successes.

So your attitude towards life was optimism?

Yes that was my attitude. I was never afraid of diseases, danger, or of dying. That comes out well from my letters, all 1500 of them.

Do you think that Italian science can compete on the world scene?

We have excellent scientists but very few. We have the problem in Italy that there is a group with power, which then decides positions not according to merit but rather based on what group the applicants belong to. There are excellent scientists in Italy, but they are not the ones who have the best possibilities because they do not belong to this or other group, Catholic group, for example. The power is in the hands of people who are politicians, not scientists.

What was your greatest challenge in your life?

I don't really know. My work went so easily. It happened so much better than I ever expected it that it was not a challenge. Everything was going so smoothly when I was young. All was so much above my hope.

What is the way to success?

I never cared about success. In the letters I wrote to my mother and also to Professor Levi, you can read that I was already considered for the Nobel Prize when I was very young, in 1962. That time I was 53 but I wrote them that this was a total nonsense, I would never receive it and I did not care about it either. Eventually I received it in 1986 — when I was 77. If you read my book you could read how I felt that time; when I went to Stockholm to receive the prize, it was not really me who was there.

It seems appropriate to quote here the relevant pages from Dr. Levi-Montalcini's book, In Praise of Imperfection*:*

"It was in the anticipatory, pre-Carnival atmosphere of Rio de Janeiro that in 1952 NGF lifted its mask to reveal its miraculous ability to cause the growth, in the space of a few hours, of dense auras of nervous fibers. Thus began its saga.

"On Christmas Eve 1986, NGF appeared in public under large floodlights, amid the splendor of a vast hall adorned for celebration, in the presence of royals of Sweden, of princes, of ladies in rich and gala dresses, and gentlemen in tuxedos. Wrapped in a black mantle, he bowed before the king and, for a moment, lowered the veil covering his face. We recognized each other in a matter of seconds when I saw him looking for me among

the applauding crowd. He then replaced his veil and disappeared as suddenly as he had appeared. ... Will we see each other again? Or was that instant the fulfillment of my desire of many years to meet him, and I have henceforth lost trace of him forever?"

Lars Ernster (courtesy of Edit Ernster).

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Lars Ernster

Lars Ernster (1920, Budapest, Hungary — 1998 Stockholm, Sweden) was Professor Emeritus of the Department of Biochemistry, Arrhenius Laboratories for Natural Sciences, Stockholm University at the time of recording our conversation on October 11, 1996. He was active in his scientific work and international interactions to the very last day of his life.

Lars Ernster and his wife Edit moved to Sweden in 1946, he received his Ph.D. from Stockholm University in 1956. His main research areas were biochemistry and cell biology, especially bioenergetics; membrane biochemistry; free radicals; antioxidants; mitochondrial diseases; and biochemical toxicology. He was a Member of the Royal Swedish Academy of Sciences as well as other societies, including the American Academy of Arts and Sciences. He held high offices in various international organizations, including the General Secretary of the International Council of Scientific Unions. He was a Member of the Nobel Committee for Chemistry from 1977 to 1988, and a Member of the Board of Trustees of the Nobel Foundation in 1990–1991.

Let's start with your family background and your education, and how did it happen that you completed your studies relatively late?

I was born in Budapest in 1920. My father was a medical doctor, a general practitioner. He died at the age of 48 when I was 16. It was the depression in Hungary just as everywhere in the world and the political situation was getting worse and worse because Nazi Germany was already a fact.

I was in the 6th grade of the Hungarian gymnasium when my father died and my schoolmates noticed that we were in a difficult situation, and they asked me to tutor them. This became quite an occupation for me. It was not charity either. They could really use my help and I did it for very little money.

I graduated from high school in 1938, but I could not get into a university in Hungary. We were Jewish and *numerus clausus* was actually changed to *numerus nullus* in 1930 as far as medical faculties were concerned and I wanted to become a physician. So I decided with a classmate of mine to go to Paris to study at the Sorbonne, and this is what we did. In Paris, we worked in the evenings; I tried to sell watches by knocking at doors for a firm, my friend worked in a garage, so we did what we could not to starve.

When the war broke out, the French ordered us to leave. I went to the Hungarian consulate to validate my passport. They said that I could not go through Germany because the bridge through the Rhine was already blown up and I cannot go through Switzerland because the Swiss do not let transit people into their country. The only way to go was Italy but for crossing Italy I needed a passport in which there was no indication of my religion. Actually the consul did not even understand how could I get out with that passport. So they gave me a new passport, without indication of my religion and through a very adventurous journey through Turin and Milan I returned to Budapest. We were in Italy on September 3 when the war broke out in Italy and there was a big demonstration against the war in Milan.

Back in Budapest, I found a job in a Jewish hospital as a laboratory technician till 1941. Then I was called for forced labor service for three months and then went back to the hospital till 1943. At the hospital laboratory I learned a lot of things, how to measure blood sugar, how to make a urine analysis. I already had some background from my studies in Paris. Originally there was a medical doctor and two lab technicians in the hospital laboratory, but when the doctor was called to forced labor, only the two of us technicians remained and we knew enough so we could run the lab. We did not get one penny for all this because this was a voluntary job. I worked from 9 to 2 in the afternoon and then I continued my tutoring to earn some money. In November 1944, the arrow-cross people killed every single person in that hospital but by then I was already at the Swedish Embassy.

I met Edit, my wife, in 1941. We decided to get married shortly afterwards but this did not happen until after the German occupation of Hungary, which took place on March 19, 1944. We married on the 5th of May during a bomb raid, and a non-Jewish friend of ours came with us to hide our yellow David stars. One month after we got married, in June of 1944, my father-in-law was called by the Swedish legation and was told that they had been authorized to issue a provisional Swedish passport to him and his family. My father-in-law was the executive managing director of the Orion radio-company and they had a good business relationship with Sweden. The whole family, including myself, moved to the Swedish Embassy. This was in June. In July, Raoul Wallenberg arrived in Budapest on his humanitarian mission to save Jewish lives. My father-in-law was one of his closest associates during those six months he operated in Budapest, till January 1945. Thousands of Swedish documents were issued to save people.

Before the end of the war, we had to move into the cellar of a bank, which was under Swedish protection. Wallenberg, his secretary, his driver, and my whole family lived in that cellar.. On the 17th of January, the Russians were already only a few streets away from us so Wallenberg decided to go over and get in touch with them to inform the Russian commander about what was going on here. He said good bye, and we never saw him again.

Raoul Wallenberg (1912–19??) in Budapest in 1944, photograph by Tamás Veres, Budapest, on November 26, 1944 (courtesy of Edit Ernster).

Lars and Edit Ernster in Stockholm (courtesy of Edit Ernster).

What is your recollection about who tried to find Wallenberg and how?

We came to Stockholm in April 1946 and by then all other members of the Swedish Embassy had returned there via Russia, except Wallenberg. First we thought that something may have happened to him on his way from Budapest to Debrecen, a city about 200 kilometers east of Budapest. We knew that he planned to go there to see the new Hungarian Government that was organized there while Budapest was still in German hands. The Russian commander's office was there too. He wanted to give the Russians first hand information about what has happened. During the last hundred days of the war, only in Budapest, a hundred thousand Jews were killed by the Hungarian arrow-cross people. The victims were just lined up at the banks of the Danube, shot, and thrown into the river. The Germans came to Hungary in March 1944, the deportation of Jews to concentration camps from all over the country, except Budapest, started in April. They were running out of time and there was no mass deportation from Budapest

and this is why the Swedes could interfere. In Budapest we had to put on the yellow David star on the 3rd of April and in May we had to move into so-called yellow-star houses. We lived there when the word came to my father-in-law from Sweden that we can move to the Swedish Embassy.

I remember an incident in November 1944 when I foolishly left the Swedish Embassy without telling anybody about it. I just wanted to meet Edit who went to a doctor. Across the street there was an arrow-cross guy standing in front of a house, he captured me and took me into the house. I asked him, "How old are you?" He said, "I am 16 and I am a student. But now during the day I am involved with capturing people and in the evening we shoot them into the Danube." I asked him, "What will happen to me?" He laughed, "You can guess!" he said. I told him about my papers, but he did not let me show them.

It turned out that they noticed my absence at the Embassy and started to search for me and they found that I was in this house. Around 5 in the afternoon they called me into the commander's office and he told the young boy to take me back to the Embassy building. But this whole incident showed me what people could really turn into. There was this young boy and I asked him, if you had gone to school today what would have been the subjects today? He said, well, first we would have had mathematics, then history, and so on. And you don't like to go to school, I asked. No, because I am doing my real duty here and this is more important. This was the general attitude.

When I got back to the Embassy, Wallenberg yelled at me, "How could you do this? You have your job here, do you have any idea what hell it was for us to find you?" So Wallenberg personally saved my life.

What was driving him?

He was 32 and came from a very famous banker family. I think that he was working here, in Stockholm, in a commercial office that had Hungarian contacts. The head of that company suggested to the foreign office to choose him to send to Hungary as someone well suited for the job due to his many Hungarian connections and his interest in humanitarian matters.

Sweden has been criticized for its behavior during the war and yet here we have the example of Wallenberg who sacrificed himself, going much beyond any possible call of duty. And he had been asked by the Swedish State to go there. How did this happen?

Sweden was one of the few neutral countries during the war. These countries had to balance their political actions somehow. I think this was part of this balance. There was a strong feeling that something should be done in terms of humanitarian actions. It was not only the Swedes who did this, the Swiss did similar things in Budapest, even the Vatican did it. The Red Cross was also there and for a short while even the Spanish, and also the Italians, but the Swedes started it. It is interesting why they started it in spite of the fact that there was a divided opinion in Sweden about political stands during the war but it did not exclude this kind of actions.

When did you continue your studies?

We went to Sweden in April 1946. First I got a job as a technician at the Wenner-Gren Institute. Then, I entered the University in 1948. At that time it was impossible for a foreigner to enter medical school in Sweden, so I decided to study something else. I thought that I could keep my job and start studying something that you can do besides working and that was mathematics. But after a few months I realized that that was not for me. So then I decided studying chemistry. I got my Master's degree in December 1953.

I continued working at the Wenner-Gren Institute. Edit worked at an insurance company because she could not get a position as a musician, the labor union was very strong. She just played behind the curtain when there was a need for it. When we became Swedish citizens in 1951, Edit got a job at the Opera as the first female member of the 450-year-old Stockholm Opera orchestra. A year later she became concertmaster. In 1954, I already had enough publications to get my next degree. Then in 1956, I got my doctor's degree.

Judging from your publications, your research production from then on looks like an explosion.

No, I would not characterize it as an explosion. When I got my doctor's degree, I got all the highest marks and that meant that I could immediately apply for an associate professor's job. I was lucky because there was one available. I worked there for 6 years like in a paradise, since I was sharing a research grant with my former supervisor, Olof Lindberg, who was a very close friend of mine. He became the director of the Wenner-Gren Institute and I took over the Physiological Chemistry Department.

Lars Ernster and Olof Lindberg in the early 1950s (courtesy of Edit Ernster).

When did you become a professor?

In 1967. In the meantime I applied for jobs in many places, at Uppsala, at Goteborg, at the Karolinska Institute. I had excellent qualifications, but the problem was always that the available positions were too specific. So I decided to do more studies and got another degree in biochemistry and yet another in analytical chemistry. After a few years I got the chair position in biochemistry at the Royal Institute of Technology. Then, after about half a year I moved to the University of Stockholm and I stayed there from 1967 to 1986 when I retired as Professor Emeritus.

How would you characterize your research activities and what areas would you single out where you did your most important contributions?

I think that biochemists can be divided into two classes, the drilling type and the digging type. The drilling type is the one who closes down on one problem. There is then the other type, the digging type that takes a shovel and starts digging. When a storm comes he turns around and starts digging elsewhere, and in doing so he somehow stumbles on something. This is the serendipity kind of scientist. I am this type.

I started out when Olov Lindberg became my supervisor. He had just come back from the United States where he had been working with the Coris, Carl and Gerty, who received the Nobel Prize the following year, in 1947. Actually several people working in that lab became later Nobel laureates. One of them was Arthur Kornberg who worked together with Lindberg on adenosine triphosphate, ATP. It is the energy currency in all our living cells. When we eat, respire, burn our food, we convert the energy that is released into forming ATP from adenosine diphosphate, ADP. The ATP is the source of energy for muscle contraction, cell division, metabolic processes, for everything.

I have become interested in ATP function and in ATP synthesis. Mitochondrion was discovered in 1946 to be the site of ATP synthesis in the cell. Mitochondria are small bodies in the plant and animal cells. This is part of a very big topic called *bioenergetics*. This is my main field and people associate my name with this field. Cell respiration, photosynthesis, metabolic diseases, and energy metabolism all belong to bioenergetics. I could not pinpoint any major discoveries I have made, so you don't find my name in the biochemistry textbooks. It is usually the names of the drilling type that get into the textbooks.

Let me mention Albert Szent-Györgyi though. He started out as a medical doctor. He was interested in biochemistry, in muscle contraction, in ATP function because it drives muscle contraction. Then he became interested in how ATP was made, how is energy converted, and so on. He was definitely a digging type. He made discoveries one after the other, by serendipity.

Without claiming a direct comparison with Albert Szent-Györgyi, I have also had a diverse interest even though I have stuck very much to bioenergetics. However, on my way I happened to discover, by serendipity, a number of reactions and enzymes.

There is a typical story. There was this young Italian fellow, Franco Navazio, working with me in 1958. One day Lindberg came into my

Lars Ernster with Albert Szent-Györgyi (1893–1986, Nobel Prize in Physiology or Medicine for 1937) in Woods Hole, Massachusetts, shortly before Szent-Györgyi's death (courtesy of Edit Ernster).

office and told me about the forthcoming visit of Professor Severin from Moscow. He wanted to show our guest our brand new D2 Beckman Spectrophotometer. It was our first recording spectrophotometer. At that time Navazio and I were working on the determination of the place in the cell where the reduced forms of the two pyridine nucleotides, NAD^+ (nicotinamide adenine dinucleotide) and $NADP^+$ (nicotinamide adenine dinucleotide phosphate), are oxidized. We know that respiration uses them, and in the microsomes there are a number of enzymes that use them. We also knew that membrane structures have these enzymes so we were looking at mitochondria and microsomes and we were following them in the spectrophotometer.

I asked Navazio to show Professor Severin the spectrophotometer in operation. Severin was obviously very impressed by what Navazio showed him. However, when he left, Navazio told me that he had forgot to put the mitochondria or the microsomes in the instrument but that he put a faction of the cell that was not supposed to have NAD or NADP, and yet it showed a tremendous activity. It turned out that we discovered an important enzyme in detoxification of quinones in the body. This is the only enzyme in this group of catalysts, which can reduce a quinone with two electrons at the same time. If you reduce a quinone to a semiquinone, it immediately reacts with oxygen, and gives rise to an oxygen radical. Such an oxygen radical can damage cells. This enzyme can reduce the

quinones by two electrons at once and thus keep them nontoxic. We gave it the name DT Diaphorase, diphospho-triphospho-pyridine-nucleotide-dihydrogen [1, 2].

There is yet another use of this enzyme. Anticancer drugs are frequently used in cancer-chemotherapy to give either a quinone or nitro-compound to the patient. They are accompanied by terrible suffering because of the side effects. It turns out that these compounds act only when they are reduced with two electrons. For some strange reason cancer cells have an abundance of this enzyme, this is why these compounds are anticancer compounds. So this enzyme is used in cancer chemotherapy by the body! The pharmaceutical companies have to search for a compound that you have to take but the enzyme has to work on it to make it toxic for DNA, that is, to make it capable to bind to DNA. Today this enzyme is very much involved in producing an anticancer drug. What we are working now on together with George Olah in Los Angeles is to devise compounds that are even better substrates for this enzyme that can very efficiently react with it.

The discovery of this enzyme is another example of serendipity. It happened in 1958 and it has stayed with me ever since, just on and off. Even my retirement symposium was devoted to this enzyme in 1986.

The use of DT Diaphorase in cancer therapy, however, was not our discovery. The story is typical of my career in that we had had a discovery, which later turned out to be very interesting for a number of reasons, which I didn't even dream about. This digging type research can be very exciting even though it may not be as precise, as thorough, and as predictably rewarding as the other type. I am mentioned whenever DT Diaphorase is mentioned and I used to have very high citation numbers. However, I am not mentioned in textbooks. Those of my colleagues, who discover an enzyme *and* go after it to the very bottom, are devoted whole chapters in textbooks.

You have been greatly involved in antioxidant materials research. Is there any relevance to our diet?

This has become a very active field. We have to use oxygen to survive, and the emergence of free radicals, that is, partially reduced oxygen, is unavoidable. Oxygen is reduced to water in respiration. That requires four electrons. If we add one electron at a time, we get free radicals. That may be superoxide radical, hydrogenperoxide, hydroxy radical, and in the

presence of light we get singlet oxygen. All these species can attack lipids, proteins, nucleic acids. Therefore the organism must be equipped to protect itself against the free radical attacks. Many diseases and even the normal process of aging and cell death is caused by reactive oxygen species. When the amount of reactive oxygen species exceeds a certain level, we have to defend ourselves. There are a number of antioxidant mechanisms built in into our body. They are also adjusted to the actual need. When we take deeper breathe while running, or we need more oxygen because we are oxidizing some drugs, or have to activate our metabolism for any reason, we have to compensate the free radical formation by antioxidant compounds. They are either formed in the organism or may come from the outside in the form of vitamins, such as Vitamins C, D and E.

This is a growing field of research because many diseases as well as the normal process of aging are induced by overproduction of reactive oxygen species. I had got involved in this, again, by serendipity. I happened to be studying DT Diaphorase, an antioxidant enzyme, and coenzyme Q, which is a quinone and which acts as antioxidant in its reduced form. Mitochondria are the main producers of oxygen radicals. We happened to be the first group to describe a mitochondrial disease, and we did this together with people at the Karolinska Institute in 1959. The disease is called Luft's disease after Rolf Luft, the clinician who led us into this field. Since then mitochondrial research has grown. In 1994, we had a Nobel Symposium on this topic, and have published its proceedings.

How about the diet?

One has to observe two things. One is that antioxidants are produced by the body itself. Normally we compensate for our needs by a fine-tuned regulatory mechanism. Unfortunately its effectiveness diminishes with age. The various symptoms of aging, for example, that we respire less, our heart function decreases, is due to the deficiency of this regulatory mechanism.

You cannot cure things with antioxidants, you can only prevent things. You can prevent degeneration, you can prevent arterial sclerosis, you can prevent aging symptoms or delay them, by antioxidants. The processes may be endogenous or exogenous. They are endogenous when we regulate them ourselves and we must understand the factors that participate; there is a number of enzymes, like coenzyme Q and others. They are exogenous when the regulators come from external sources, like Vitamin C, Vitamin E, beta-karotin, flavonoids, and so on, that we eat.

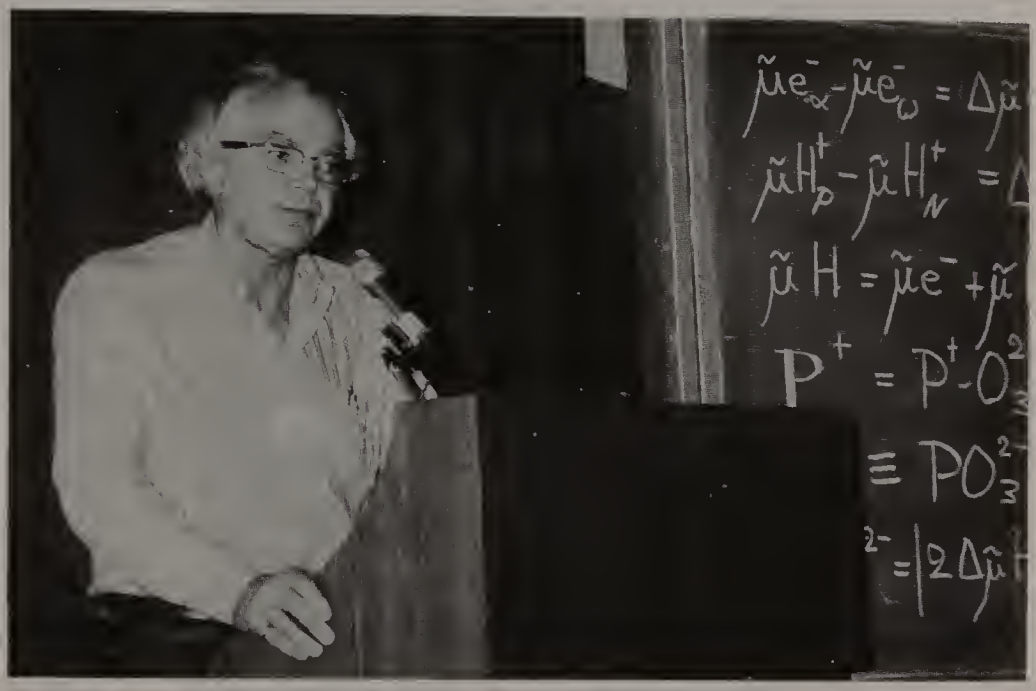
The question is how to know what and how much to take. We have to remember one thing, whenever we use an antioxidant, chemically speaking, it quenches a free radical but by doing so, it becomes itself a free radical. So the free radical produced by the antioxidant must be stable or must be capable of regenerating the antioxidant. We strongly advocate that we cannot apply the rule that ten times more is ten times better. We have an antioxidant task force in the International Life Sciences Institute, and we try to determine the right amounts of various antioxidants. For this we need to know the mechanism of their efforts and also the situation in which they are being employed.

How about Vitamin C?

Of course, Linus Pauling was famous for eating 18 grams of Vitamin C daily. He believed in it and lived until the age of 93. However, I would suggest caution when large doses of iron and large doses of Vitamin C are used simultaneously. I recommend various control measures, monitoring blood levels, antioxidant levels. If the effect does not increase above a certain level, why take more? It is excreted by the organism anyway. However, regardless of excesses, Linus Pauling was a true pioneer with his notion of molecular disease. What we have learned, following his contributions, is that there are two sides of the coin, that antioxidants are potential prooxidants, and that combination effects should not be ignored. Taking 18 grams of Vitamin C is all right but taking it simultaneously with large amounts of iron may be damaging. This is now becoming a big field, applied biochemistry and molecular medicine. I am excited by this field because it gives so many opportunities to make basic knowledge available to practical use.

In my preparation for this conversation I did some reading of papers and books in your field and got the impression that you have been influential and even popular among your peers.

Popular, probably, yes. Of course, you can become popular in different ways. Bioenergetics was famous for having tremendous fights in the 1960s and 1970s. You can find symposium volumes in which almost half of the text is devoted to discussions. People were saying fantastic things to each other, in a very educated way. Bioenergetics used to be the maverick of biochemistry. So popular may not be the appropriate term for me either but perhaps notorious. I stood up at a meeting and said, "I don't believe



Peter Mitchell (1920–1992), Nobel laureate in Chemistry, 1978, "for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory" (courtesy of Edit Ernster).

in Peter Mitchell." Then, half a year later I would say, "Now I am beginning to believe him because I had seen his experiment."

Incidentally, Mitchell was a great thinker and a great personality. He received the 1978 Nobel Prize in Chemistry but is not very well known among chemists. He was one of those borderline cases in the history of the Nobel Prizes for whom there could have been an equal justification to receive the Nobel Prize in Physiology or Medicine, rather than in chemistry. He is not the only example of this. Biochemistry, after all, is on the borderline between biology and chemistry, and biology is a very important part of physiology and medicine.

There is no Nobel Prize in Biology.

No. Nobel's Testament clearly states that one prize should be given in chemistry and one in physiology or medicine. Most probably what Nobel or the ones who advised him on this point meant by physiology or medicine included biology. You shouldn't forget that biochemistry is a science of the 20th century, and Nobel's Testament was written before the beginning of this century. The first Nobel Prize was given in 1901. Biochemistry

as such was not really on the map. We have to assume that chemistry is chemistry and physiology or medicine is sort of biology. If there is a discovery in biochemistry, the decision is very difficult whether it should be awarded the chemistry prize or the physiology or medicine prize. I can only mention one example, John Kendrew and Max Perutz got the prize in chemistry for their studies of the structure of globular proteins. In the same year Francis Crick, James Watson, and Maurice Wilkins got the prize in physiology or medicine for their discoveries concerning the molecular structure of nucleic acids. Why not the other way around? This example clearly shows that the division line is very blurred.

Do these two Nobel Prize committees cooperate?

There is no formal mechanism for that; but they maintain contact. It should be avoided that someone is passed over by one committee because it is assumed that the other committee is awarding that particular discovery. It should also be avoided that the same person be given two prizes for the same discovery by two committees.

Do you think that the digging type or the drilling type researcher has a greater chance of receiving the prize?

Difficult to say and I have never even attempted to make a statistics. But let me give you an example. Severo Ochoa got the Nobel Prize in Physiology or Medicine in 1959 for his contribution to nucleic acid synthesis. Prior to the discovery for which Ochoa got the Prize, he was entirely engaged with oxidative phosphorylation, bioenergetics. He was one of the pioneers in the field in the early 1940s. Ten years later one day his technician told Ochoa that the ^{32}P completely disappeared from the sample they were studying. The technician had just carried out the usual routine to separate the protein precipitate and extract the ATP to measure radioactivity. They found the phosphorus in the precipitate, which contained not only the protein but also nucleic acids. This accidental observation led Ochoa to his prize-winning discovery, and it was another example of serendipity.

Arthur Kornberg shared the 1959 Nobel Prize in Physiology or Medicine with Ochoa. He was one of the greatest names in the history of biochemistry. He worked at Washington University in St. Louis. He got interested in oxidative phosphorylation through Carl Cori who was the Head of the Laboratory. Carl Cori and his wife, Gerty Cori got the Nobel Prize in

From the award ceremony on December 10, 1978. Lars Ernster, as the representative of the chemistry Nobel Committee is behind Queen Sylvia (courtesy of Edit Ernster).

Physiology or Medicine in 1947 for their work on the catalytic conversion of glycogen. I visited Kornberg together with Olov Lindberg in November 1955 and it was my first visit to the United States. Kornberg told me a story of his wife and coworker, Sylvy, one day telling him about the synthesis of a new substance. They first thought it was DNA but it turned out to be a polyphosphate material. Sylvy had died long ago but Arthur returned to the polyphosphate synthesis after retirement. He is in his eighties now and gave a seminar recently in our Institute on the polyphosphate synthesis. Arthur and Sylvy did indeed synthesize DNA only weeks after our visit. Their next project was the isolation and purification of the enzyme that makes DNA, DNA Polymerase. This was what he got the prize for in 1959. So this was another serendipity story. But you must have a prepared mind.

As Louis Pasteur said.

And he said something else too. He said, whenever you try to understand a biological phenomenon, find an organism in which nature has exaggerated it. So, for example, if you want to understand fermentation, you must go to yeast.

Did you ever get close to doing Nobel Prize level work?

No. I have been very far from it.

Did it make it easier for you to judge and evaluate other peoples' contributions?

This is something I have never thought about.

You must have a tremendous overview of your field when you work on the Nobel Prize recommendations.

What sitting on the Nobel Committee gave me most of all was that I tried to understand and developed a respect for other fields, different from mine. It was also obvious that we should not try to become experts in other fields, to the extent that we could make judgments. It would be both pretentious and futile. What I tried to do was to understand, appreciate, and respect the opinion of my colleagues.

I have heard a criticism that Avery, MacLeod, and McCarthy should have received the Nobel Prize for discovering the transforming principle, the fact that the genetic material is a nucleic acid, DNA.

This is not my field, moreover, it is more physiology or medicine rather than chemistry. However, there are very important discoveries in the history of chemistry in general and biochemistry in particular, which have not been awarded. I do believe this is so. The explanation is not simple. David Keilin, for example, should have got the Nobel Prize for the discovery of cytochromes. The discovery of ATP, in 1929 by Karl Lohman in Germany should have been awarded. The excuse is very simple. Karl Lohman described it in a three quarters of a page paper in *Naturwissenschaften* and said this was the nature of the organic phosphate bound to muscle fibers. He did not draw any conclusions about its role; just identified this mysterious substance found in muscle fibers. Then a year later Engelhardt in Russia discovered oxidative phosphorylation in respiration. Neither of them received

the Nobel Prize. Then Otto Warburg in Germany described ATP's role in glycolysis. Warburg received the Nobel Prize in Physiology or Medicine in 1931 for his discovery of the nature and action of respiratory enzyme. Later Fritz Lipmann in the United States discovered that ATP was the high-energy phosphate. He did receive the Nobel Prize in Physiology or Medicine in 1953, but not for this discovery, for something else, for coenzyme A and for the understanding of its importance for intermediary metabolism. I can explain every one of the missing Nobel Prizes. Lohman discovered ATP but he didn't recognize its function. Engelhardt discovered oxidative phosphorylation but it was not easy at that time to identify the product with ATP. Warburg described oxidative phosphorylation, but got the prize for something else. Keilin didn't get the Nobel Prize because they said, it's true that he discovered cytochromes but there were some hemoproteins already discovered in 1879 by others who thought it was hemoglobin although it was not.

Now I am talking about my own field but I'm sure others working in other fields could pinpoint similar cases; discoveries that have proved to be as important as those that have been awarded. You cannot be perfect.

How about the division of biochemistry Nobel Prizes between Chemistry and Physiology or Medicine.

Some chemists may feel that the discoveries in biochemistry are not that important for new chemical concepts. However, biology has opened up fields of chemistry that never would have been opened up by chemists alone. Had not it been for biochemistry, where is the organic chemist who would have conceived the concept of proteins. Has it ever occurred to an organic chemist that there are molecules composed of one thousand amino acids connected with peptide bonds. We learned about these molecules because biochemists had isolated them from nature, and characterized them. There has been a great conceptual contribution by biology to chemistry. We are truly talking about new *chemical* concepts. When we hear this argument that we are giving out too many prizes to biochemists, we always have to remember this.

The Nobel Prize has reached such an improbable high prestige that you may develop some skepticism whether any discovery is important enough to be awarded. On the other hand, every year there are many expectations and, inevitably, many disappointments.

Of course, we absolutely have to rely upon the opinion of experts, but for the broader community, there is never any opinion poll. No campaign, no lobbying, and no opinion research. Nobody goes around with the question, "What do you think?" or, "How would you react?"

There is then another problem. Nobel's Testament says that the Prize should be given for the most important discovery of the year. However, it is reasonable to wait for a while to see the importance of the discovery. It happens that an old discovery becomes truly significant many years later only. In this sense old discoveries may also become candidates. There is then the difficulty of suddenly too many names popping up, making the situation impossible.

You have been involved in international science organizations.

I got involved in 1963 when, at Jacques Monod's initiative, we started the International Cell Research Organization (ICRO) under UNESCO. We have organized international training courses at an advanced level for students in cell biology. Eventually I became President of ICRO. When I stepped down, they elected me lifetime Honorary President.

There is then this big umbrella organization ICSU, International Council of Scientific Unions. I served as its Secretary General between 1982 and 1988. Although it was not a full time job, it meant daily commitment. The headquarters is in Paris and I made at least 50 trips to Paris during those six years. I found it a very stimulating appointment. For the first time I felt my head above the ditch, seeing fields that I had never seen before. In 1984, the International Life Sciences Institute, originally created by the Coca Cola Company, asked me to become the President of its European Branch. This organization promotes collaborative efforts between industries and academic science. I served in this post from 1986 to 1994. I resigned because I believe that no position should be held longer than eight years.

You have had a very exciting life. You were a latecomer in science but your research activities burst into the international scene with a large amount of results and recognition. Looking now back, if you had the magic possibility, how would you have preferred charting your life?

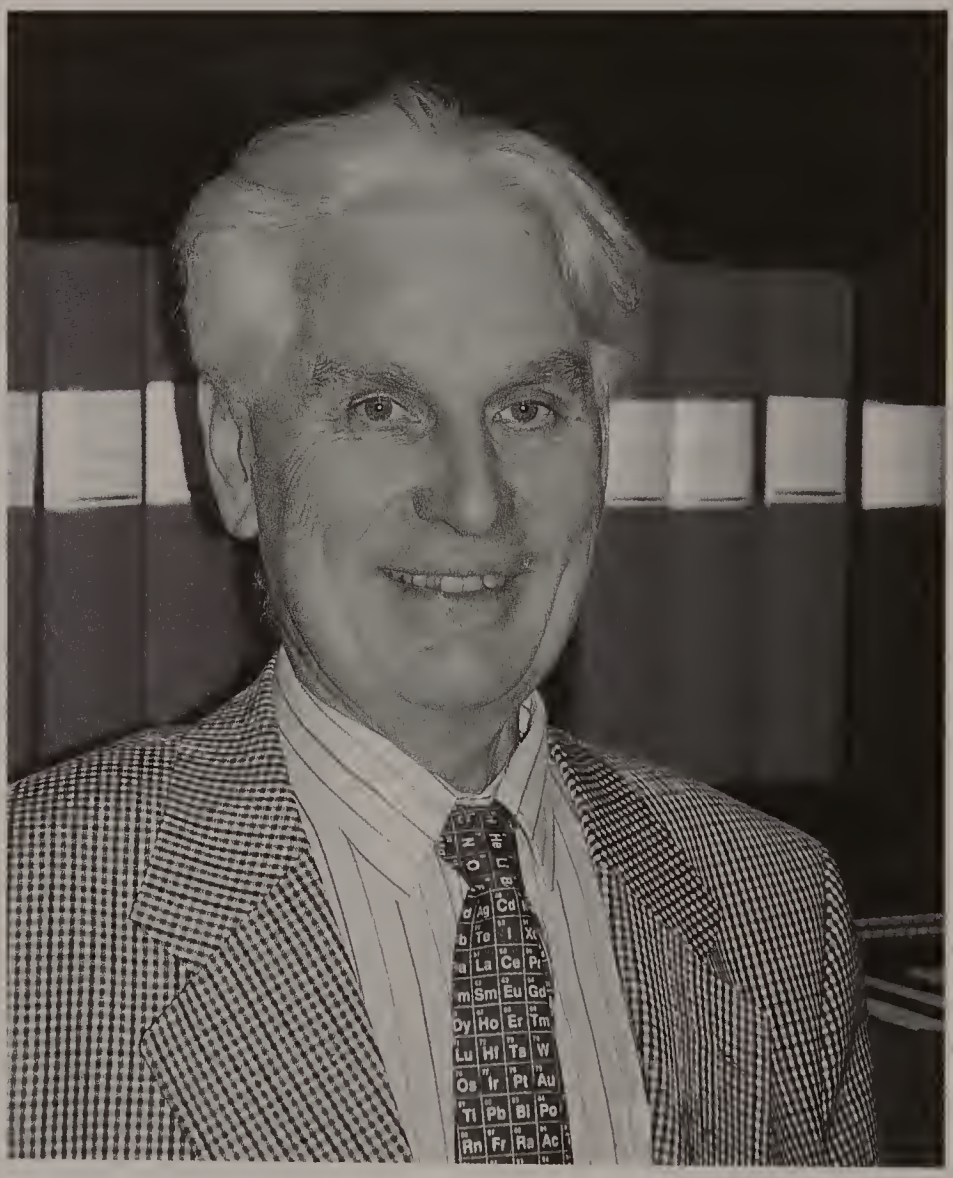
Had my career not started in a highly hindered way in Hungary, I would have concentrated on becoming a medical doctor. I would have done everything to do some good medicine. That was my original goal. I had been observing from my early childhood my father, who was a medical

doctor, curing patients and the satisfaction of that. My dream was to emulate him.

In retrospect, I have been very fortunate. I could open up internationally, I saw the world, I got a broad intellectual horizon. On top of this, my wife, Edit, is an artist and she gave me a whole different perspective of life, in addition to science. I couldn't have done better.

References

1. Ernster, L.; Navazio, F. "Soluble Diaphorase in Animal Tissues," *Acta Chem. Scand.* **1958**, *12*, 595.
2. Ernster, L. "DT Diaphorase: A Historical Review," *Chemica Scripta* **1987**, *27A*, 1–13.



Torvard C. Laurent, 1997 (photograph by I. Hargittai).

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Torvard C. Laurent

Torvard C. Laurent (b. 1930 in Stockholm, Sweden) is Professor Emeritus of Medical and Physiological Chemistry at the University of Uppsala. He was educated at the Karolinska Institute in Stockholm. He is a Member and former President of the Royal Swedish Academy of Sciences. He is currently a Member of the Nobel Committee for Chemistry and Chairman of the Council of the Nobel Foundation. He is also Scientific Secretary of the Wenner-Gren Foundation. Professor Laurent is a Member of the Academia Europaea (London) and the Academia Scientiarum et Artium Europea (Salzburg). He has been much decorated and has received many honors, including the King Carl XVI Gustaf's Gold Medal in 1994.

Professor Laurent's research has concerned the chemistry of connective tissue, especially the physical properties, physiological functions, turnover, and medical applications of the polysaccharide hyaluronan; ophthalmic biochemistry; physical chemistry of polysaccharide networks, especially transport processes in polysaccharide solutions; and biochemical separation techniques, including a theory of gel filtration and methods for cell separation.

We recorded our conversation in October 1996, during my Wenner-Gren Lectureship in Sweden, and then finalized the material in August 1997, in Uppsala.*

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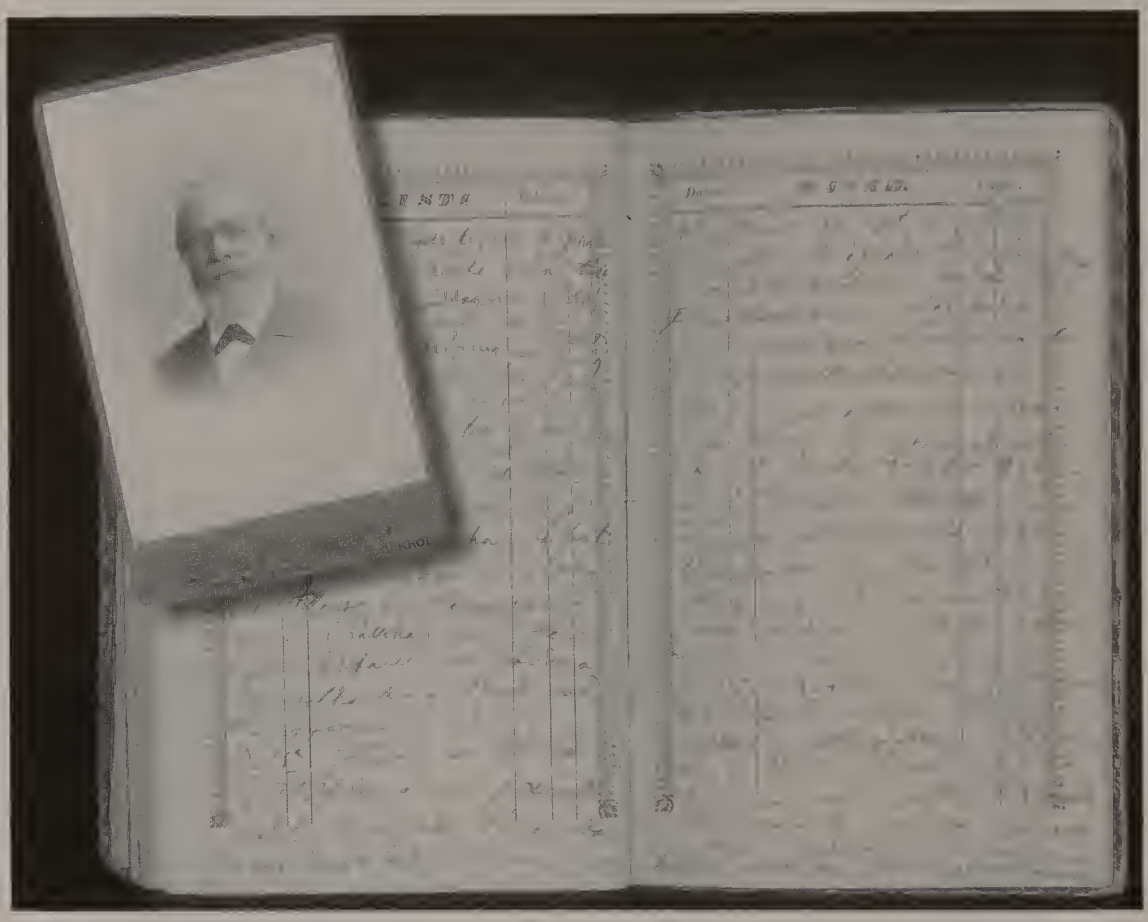

Carl-Eric Bergstrand (1830–1914), the great-grandfather of Torvard Laurent. Bergstrand became Professor of Agricultural Chemistry in 1864 and worked at Ultuna (now the Swedish Agricultural University). He subsequently became head of the Chemical Research Station of the Academy of Agricultural Sciences in Stockholm (1869–1882). His main research was in fertilizers. In the summer of 1859, he received money from the King for a tour of study in Germany and Austria. He visited a large number of laboratories and met the most well-known German chemists at that time. The photo shows pages from his diary in which he describes his visit to Friedrich Wöhler in Göttingen on August 15 and 16 (composite photograph by Gustaf Hellsing, courtesy of Torvard Laurent).

Let's start with your background, your family, your education, and your route to scientific research.

I come from an academic family. My father's maternal grandfather started as a poor boy on a farm and fought his way to become a Professor of Agricultural Chemistry in Stockholm. His son was a Professor of Astronomy, and my father was Professor of Telecommunications. My older brother was a Professor of Theoretical Physics in Stockholm. Thus, it is not surprising that I chose science, although I did not intend to become a chemist.

When I entered medical school, at the Karolinska Institute in Stockholm, I was 17. I had anatomy and histology during the first year and the Professor of Experimental Histology invited me to become an unpaid instructor. I started this work at 18, and I was working with a Hungarian guest scientist, Endre Balazs. He came to Sweden in 1947 to attend an international meeting on cytology and stayed in Sweden. He was anticipating the imminent Soviet takeover in Hungary. Balazs was very interested in the effects of polysaccharides on the growth and multiplication of cells and had started this work in Hungary. I started working with him in 1949. He was doing cell culturing, and at that time very few people were doing this. This was before antibiotics were used in such research, and everything had to be done under absolutely sterile conditions. I had to prepare the polysaccharides from tissues. In this case the polysaccharide was hyaluronic acid (nowadays called hyaluronan), which can be found in umbilical cords. So I went to the hospital, picked up the umbilical cords, and extracted the polysaccharide, which is of high molecular weight.

During this work I made observations that led to publications already at that time. The first was that if the extraction was done with water, I got a much higher viscosity than when physiological salt solution was used. Today this would not surprise anybody, but at that time it was very surprising. The other observation resulted from our attempts to sterilize the polysaccharide. We could not filter it because it was too viscous. We decided to sterilize it with ultraviolet light. When we did this, the high viscosity disappeared; as we learned later, this was due to the degrading impact of irradiation. What happened was that the irradiation generated hydroxy free radicals, and they attacked the polysaccharide chain. This process has been studied a lot ever since. We didn't know about the mechanism at that time; we just made the observation.

We then made yet another observation. We wanted to use hyaluronic acid in the cell culture to see if it had an effect on growth. We run parallel

experiments with other polysaccharides, including hyaluronic acid that had been synthetically sulfated. We thought that if we sulfated it, we would get heparin, another polysaccharide with interesting anticoagulant activities containing the same sugars as hyaluronic acid. The sulfated hyaluronic acid proved to have enzyme-inhibiting activity and had an effect on cell growth like heparin had. This gave us yet a third paper. I was 18, I was doing my studies in medicine and at the same time working with Balazs, and in 15 months this work had resulted in three research papers. I just could not stop doing this kind of research.

Endre Balazs is a very charismatic person. In 1950, he moved to Boston out of fear of the Russians being so close to Sweden, and the Korean War had just broken out. He is now 76 and has a biotechnology company in New Jersey. We just had him here a few weeks ago for a conference in his honor.

At about the time of Balazs's departure, our department was reorganized, and I moved to the Chemistry Department of the Karolinska Institute. I started working with a physical chemist, Bertil Jacobson. He was highly skilled in building instruments and eventually became Professor of Medical Electronics.

Jacobson built an instrument for measuring the dielectric constants of polyelectrolyte solutions. There were some peculiarities in the dielectric

This picture was taken at the Retina Foundation in 1953. Endre A. Balazs is to the right, Laurent is to the left (photo courtesy of Professor Laurent).

constants of nucleic acid solutions, and Jacobson thought that the formation of ice around the nucleic acid molecules might be the origin of the increased values. Ice has a larger dielectric constant than water. I made measurements on hyaluronic acid with this instrument.

Balazs asked me to join him in Boston in 1953. I was 22 at the time and had never been abroad before, had never even left my parents' home before. So my father took me to the harbor in Stockholm and put me and my trunk on board a cargo ship that sailed to Portland, Maine, where Balazs picked me up and brought me to Boston.

Balazs was building a modern research institute for ophthalmic chemistry in an old apartment house. He got the money from a retina surgeon who operated on detached retinas. The cause of retinal detachment was thought to originate in the vitreous body behind the lens in the eye, so Balazs studied the vitreous body. During this work I learned the light scattering technique for characterization of macromolecules. After half a year, Ulla came over and we got married. We had met in medical school back in Stockholm. So Ulla also worked for a year in ophthalmic chemistry. Eventually she became an ophthalmologist.

Upon our return to Stockholm, I continued with Bertil Jacobson and did X-ray diffraction on nucleic acid solutions to see if there was ordered water around the macromolecules. It was 1953, and the Watson–Crick model of the DNA double helix had just been published. Jacobson calculated that the double-helix structure could easily be accommodated in the ice/water lattice, pointing to the possibility of nucleation of an ice structure around it. However, the result of my work was that if there was any kind of ordered water structure around DNA and hyaluronic acid, it couldn't be more than one percent of the total water. This amount could never explain the dielectric properties of the solutions. Today we know that the dielectric properties are due to ion movements. Ultimately, I completed my dissertation at the Karolinska Institute and defended it in 1957. The title of my thesis was "Physico-Chemical Studies of Hyaluronic Acid." I was 26. Half a year later, I finished my medical degree (M.D.).

My professor, Einar Hammarsten, had a great influence on me. He was the father of biochemistry in Swedish medical schools. There were two main schools of biochemistry in Sweden. One was Tiselius's school here in Uppsala, which worked essentially on separation techniques. The other was the Hammarsten School at the Karolinska Institute, which was originally centered around studies of nucleic acids.

Ulla and Torvard Laurent at the Retina Foundation in Boston (courtesy of Torvard Laurent).

When Hammarsten found somebody in whom he believed, he would assist him and his work in any way he could. To my great surprise, he got money for me to buy a light scattering apparatus, and he also got me a personal assistantship in biophysical chemistry. He was extremely helpful even though if I didn't work directly under him. In spite of that, I was afraid of him. Everybody in the Department called him by his first name, Einar. However, I grew up in a family where it was unthinkable to call a professor by his first name or use the familiar form of address. So I had difficulties in talking to him at that time. Eventually, we became very good friends. The difference in our ages was 40 years. A whole elite of Swedish medical and physiological chemistry grew up under his tutelage. The more I think about him, the more I try to emulate him, and I think about him a lot.

Hammarsten never had an office. He was always at the laboratory bench. The department used his office as a coffee room. He was always walking around with a pipe in his mouth, and you couldn't hear what he said, but he decided everything and had enormous power.

Einar Hammarsten (1889–1968). Hammarsten was Professor of Chemistry and Pharmacy at the Karolinska Institute (1928–1957). His research was primarily on nucleic acids. Hammarsten has had a great influence on Swedish Medical Biochemistry primarily through his pupils. Laurent was the last graduate student from his department before he retired. The picture was taken in October 1966 after the inauguration of Laurent as a professor in Uppsala. Hammarsten to the left and the Physiologist Professor Torsten Theorell (another of Hammarsten's pupils) to the right (courtesy of Torvard Laurent).

When he retired and his successor arrived, suddenly there was no space for me in the Department anymore, and I returned to Balazs in Boston in 1959. This time we stayed for two and a half years. Balazs's institute had grown quite a bit, and there were many Swedes and Hungarians and some Americans. It was an exciting and vibrant place. The main thrust was eye research, but I continued with physical chemistry, and besides helping other people who worked on the chemistry of polysaccharides, I did my own work on the physiological function of polysaccharides in connective tissue.

I characterized hyaluronic acid as a very large molecule of a molecular weight of 4–5 million, with an enormous hydrated volume. It was like a random coil with about 1000 times more water than organic material within the coil domain. At a concentration as low as 0.1 percent, the molecules started to entangle and form three-dimensional networks in solution. I realized that this must be how these polysaccharides occur between the cells. I thus became very interested in the properties of these networks. First, I examined whether they would act as a filter for other macromolecules. I used an analytical ultracentrifuge and worked a lot on transport by sedimentation and diffusion. I found that these networks actually act as sieves. At the same time, an Oxford researcher, A. G. Ogston, had published findings that these networks sterically exclude other macromolecules. He studied the partition of protein between a buffer phase and a polysaccharide solution. The protein went to the buffer phase and was excluded from the polysaccharide phase. I also studied this process.

We returned to Sweden when there was an opening in Uppsala in 1961. As much as I liked Balazs, and he was also very successful, I thought it was better to break away from him. Such a teacher/pupil relationship must come to an end at some point. Although there was only a 10-year age difference, many people in America thought it was a father/son relationship. He had a family, of course, of his own. We have been in very close contact ever since. After he had built his institute in Boston, he moved to become Professor of Experimental Ophthalmology at Columbia University. When he retired from Columbia, he moved over to the biotechnology company he had built in New Jersey. It is called Biomatrix, Inc.

In Uppsala, I joined the Department of Medical and Physiological Chemistry. This was at a time when Swedish universities were expanding. There were more students, and money was pouring in. Research was

flourishing. It was a good time to start. I continued my work on the physical chemistry of polysaccharides. I studied the properties of their concentrated, or rather semidilute, solutions, and the relationship with their physiological functions in the body. This was my main line of research from 1961 to 1980. In 1963, the position of chair of the Department became vacant. There were 17 applicants, and I was one of them. The two-person short list consisted of Lars Ernster and myself, and then the final selection process took two and a half years, and finally I was appointed to the chair. It worked out for both of us because eventually Lars got the chair in Stockholm. I think this would have been the preference for both of us. However, if you just assess the scientific qualities and quantities, Lars Ernster was much more qualified than I was. I was young, I had published much less, and I was working in a different field. In the end what may have tipped the scale in my favor was my medical training in addition to my chemical background. It was a painful process, and we even had to write to the King about it, but the competition between us has not influenced our good friendship.

Thus, in 1966, when I was 35, I was appointed Professor. We built and expanded, and I was heavily involved in administrative duties. I got onto two different research councils for the whole of Sweden, science and medicine. All this was taxing my time, but it was also a decisive period for Swedish universities and science. What saved my research was that I had extremely good graduate students. Most of them are professors now. At some point I was contemplating a shift to neuroscience, but it just could not be done and I stayed with my biophysical chemistry line of research. However, when the administrative work seemed to overwhelm me, I took a sabbatical year and we went to Australia in 1979 to work with my friend Barry Preston on problems with which my close colleague in Uppsala, Lars-Olof Sundelöf, was also involved. I have had Australian colleagues in my lab since 1972. My wife and I and our youngest daughter spent a year at Monash University in Clayton, Victoria. It was a very happy and most fruitful year.

Our interest at that time centered on a phenomenon that Barry Preston had discovered. He had found that high-molecular-weight polyvinylpyrrolidone (PVP) "diffuses" extremely rapidly through dextran solutions — much more rapidly than glucose, for example. If you had tritium-labeled PVP of molecular weight 300,000 and ^{14}C labeled glucose in a dextran solution and layered another dextran solution on top, you could see an enormous difference

in their transport up into the top solution. The only explanation we could provide was that the large PVP molecules were excluded in this concentrated dextran solution, they acquired high chemical activity, and this was the driving force of the rapid diffusion. After a lot of frustrating unsuccessful experiments, we suddenly discovered that if we stained the PVP blue we could follow what was happening with our naked eyes. Indeed, the PVP moved up in regular fingers through the top solution. There was an ordered convection in the system. The explanation is that PVP increases the osmotic pressure so that the bottom solution takes up water from the dextran solution at the top, which leads to a density inversion and induces regular convection. Blue PVP fingers move up, and they are driven osmotically. The glucose, on the other hand, is transported by countercurrent distribution between upward- and downward-going fingers and is essentially standing still. This was a truly unexpected discovery, the kind one makes once in a lifetime.

It was also during that year in Australia that my wife started working again on the presence of hyaluronic acid in the eye, which we had worked on in Boston. It went so well that when we came back to Sweden, she could defend her doctoral thesis in ophthalmology.

We also initiated a new collaboration in Australia, and finally I switched research fields, something that I could not have done some years before. We turned to the study of the metabolism of polysaccharides, and Robert Fraser at Melbourne University became my closest collaborator for the next 15 years.

At this point I feel I have to return to Endre Balazs. He came to Uppsala in 1971 and told me that he had succeeded in making pure hyaluronic acid. Together with a Swedish orthopedic surgeon, he injected it in the knees of racehorses, which were limping because of injury, and the horses started to run. He thought that people could also be treated and was looking for an industrial contact to participate in the project. Since I had very close contacts with the pharmaceutical company Pharmacia in Uppsala, I made the connection, and they took up the project and have manufactured hyaluronic acid since then.

There was then another new development in 1979. It was the time when they started implantation of artificial lenses in the eye in cataract surgery. There was a Harvard surgeon who made experiments on rabbits. However, the plastic lenses tended to stick to the inside of the cornea. He went to Balazs, who gave him a concentrated hyaluronic acid solution. He dipped the lenses in the solution, and the problem was solved. Within

a year, the substance was put on the market as a surgical aid in ophthalmology. It is now one of Pharmacia's largest products.

In 1980, one of my graduate students had developed a technique to determine hyaluronan in nanogram amounts. So for the first time it became possible to measure it in all tissues. My wife showed in Australia that there were small amounts in blood and that it came via the lymph from the peripheral tissues. Bob Fraser then injected radioactive hyaluronan into rabbits to see how fast it disappeared from blood; he found that it disappeared with a half-life of two and a half minutes. It went to the liver. So we started a large project to study the turnover of the polysaccharide in the organism. We showed that it went into some special cells in the liver, and we even found the receptor.

Is it harmful for the liver?

Not at all, this is the normal process. This investigation has continued ever since and also turned into very interesting clinical research and provided a diagnostic tool. For example, if you find hyaluronan in high concentration in the blood, this could point to liver disease, especially a defect of some cells for which heretofore no test existed. High serum hyaluronan is always seen in liver cirrhosis.

Another disease with elevated serum hyaluronan is rheumatic arthritis. When you move the joints, which contain the polysaccharide you pump it out in the blood. When it accumulates in the joints in rheumatoid arthritis, more is pumped into the blood. The variation in concentration of hyaluronan in the blood may tell us a lot about the conditions in the joints. All this has been a very interesting and very rewarding development in the last 15 years.

A perfect example also of combining chemistry and medicine.

Absolutely perfect. And this is my scientific history.

How much was your work a continuation of the great separation science of Svedberg and Tiselius in Uppsala?

I came to Uppsala as an outsider. Svedberg was very old and I never met him although I saw him on the street sometimes. He had many children. One of his daughters was my classmate in high school. She later married the son of another Nobel laureate.

I met Tiselius and liked him very much. He was by then close to retirement, but I had close contacts with his co-workers because they were very interested in polysaccharides. Uppsala was much smaller at that time so we met a lot of other scientists socially, people from medicine and biology. There was a lot of interaction. For example, in 1964, by using our experience with connective tissue polysaccharides, we were able to propose an explanation for chromatography on dextran columns (gel filtration) developed in the biochemistry department.

Besides research, what interests you the most?

I have also been very interested in science politics. This followed from my involvement with the research councils in the 1970s. There was also a special reason. In the mid-1970s, there was suddenly an anti-academic movement in Sweden. The politicians accused us of not producing anything useful in spite of the tremendous amounts of money they had put into science. They wanted to place politicians in the research councils to give us the right directions. There was a need to defend science. Medical researchers were accused of neglecting "the gray diseases," such as knee problems, and of working on cancer only. As a result, they set up chairs of rheumatology at every university in Sweden, which was a mistake because there were not enough good people to staff these chairs immediately. I prepared a special report for the medical research council about the proper way of developing rheumatology, starting with special postdoctoral positions. After we had trained these postdocs in rheumatology, we established a six-year investigator position for them. Only then would they be ready for the chairs. As a result, Sweden is now excellent in rheumatology. There is a lesson for the politicians — a change in research direction does not happen overnight.

In 1977, the University of Uppsala had its 500th anniversary. The celebrations lasted for a whole year. At the main ceremonies Glenn T. Seaborg gave a talk. I gave the official address at the graduation ceremony and awarded the insignia to the honorary doctors of medicine. We had 100 foreign scientists receiving honorary degrees on that occasion. The main message of my talk was that modern medicine is based on basic research. I showed how, for example, discoveries in Uppsala have become important in medicine. Some of the more striking examples were the work by Celsius and Linnaeus on the development of the thermometer; the discovery of lymph vessels by Rudbeckius — the basis for immunology; the discovery

of oxygen by Scheele — the basis of respiratory physiology; the centrifugation of blood by Hedin, which led to hematocrit analyses; the development of erythocyte sedimentation rate as a diagnostic tool by Fåhraeus; the discovery of the parathyroid glands by Sandström — of importance for calcium deposition in bone; the development of electrophoresis by Tiselius, which led to the discoveries of various plasma proteins including gamma globulins; the development of dextran as a plasma substitute by Ingelman and Grönvall; and so on.

Subsequently I have been asked to discuss this topic many times and I have tried to keep up with recent developments. It is our task to educate the politicians about the mechanism and use of scientific research. There are examples from our own department of basic results finding their way into the pharmaceutical industry and becoming important even for exports. The value of exports that have originated from our department is larger than the budget of the whole Uppsala University. One example is the hyaluronan story. Another example is a low-molecular-weight heparin developed by Professor Ulf Lindahl of our department. It has become a very popular anticoagulant compound. Yet another example is an allergy diagnostic kit based on immunoglobulin E, characterized by Hans Bennich and Gunnar Johansson. There is also Protein A from *Staphylococcus aureus* purified by Professor John Sjöquist. It binds to antibodies and is used as an immunochemical reagent. We also developed Percoll, a density gradient material for cell separation.

Of course, this is all on top of the basic function of the university, which is education and production of specialists.

135 people have obtained their doctorates in our department since I came to Uppsala — about 80 of them from my group and 26 of them my personal students.

Did you succeed in convincing the politicians?

I think so — at least for a while. There is, however, a great dilemma. We used to have this great collaboration with Pharmacia, only to see it be destroyed by the industrialists. It started with Volvo, which bought up the shares of Pharmacia. Then Volvo immediately started talking about structure rationalizing the Swedish pharmaceutical industry. First, they wanted to sell Pharmacia to an Egyptian who turned out to be a fraud. Then

they started fusing it with other Swedish pharmaceutical industries. A lot of harmful internal fights emerged. Finally, Pharmacia merged with Upjohn, and as a result the company is moving all research out of Uppsala to Stockholm. I have tried to talk to responsible people, but they just wouldn't listen. I think they have destroyed something of the best of what we have had in Sweden in university/industry collaboration. I don't believe in the multinational companies any longer. They are large and bureaucratic with no clear chain of command.

At present, my main interest is to try to revive collaborative work with industry but with small companies. For the first time, I have accepted membership on the board of a minor pharmaceutical company. Since I have retired officially from my professorship at the university, there is no impropriety in this or conflict of interest. I would very much like to facilitate the exchange of ideas between the company and our department. We have had this fantastic experience of turning over ideas to Pharmacia, and I would like to do the same but now with small companies. My last experience with the Pharmacia-Upjohn people was when they told me that I was a visionary and that they needed people who understand economics.

You held the ultimate position in science politics as you were President of the Royal Swedish Academy of Sciences.

That was between 1991 and 1994. You can hold it for three years. I was elected member of the Academy in 1982. At the beginning, I was not very active, but the situation changed. At the time when I was elected President, it was also decided to delegate a member of the Medical Class to the Nobel Committee for Chemistry. I was elected for this too and have been on the Nobel Committee for Chemistry since 1992.

The Presidency of the Academy turned out to require much more work than I had expected. I had to travel, see people, sign documents, and so on. However, it was also very interesting. The most interesting facet of my work was that just at that time we got a nonsocialist government, and the new Minister of Education wanted to decentralize education. He wanted to pull out government from the higher education sector and let the universities rule themselves. But he also wanted some supervision over the universities and suggested that the Academy should take up this role. Thus, the Minister came to the Academy, but I told him that our Academy

is a private organization and we have no obligations to the government. We would, of course, be happy to help and give advice when asked but would never do anything by order.

Doesn't the state subsidize the Academy?

Very little. We used to have the so-called Almanack20 Privilege; we used to get all the proceeds from the sales of calendars in Sweden. However, Olof Palme took that away from us. Since then the government has given us an annual subsidy, but it is a minor part of our budget. The Academy lives essentially off its capital and off grants.

The Minister of Education liked what I told him, and it was exactly what he wanted — an independent organization that didn't take orders from anyone. After that, the Academy became the best partner of the government with regard to education, science, etc. For example, we have evaluated the Swedish higher educational system and made recommendations to increase the efforts in the natural sciences. There should be more emphasis on the sciences from the very first grade in primary school, and teacher competence should be increased. This is necessary if we want to maintain the interest of science-oriented children from the beginning. "The children should be exposed to science from the first grade but our teachers are not prepared for it" was our main message. The necessary changes were being contemplated when the government was voted out of office. Under the present socialist government, the relationship between the Minister of Education and the academic world has deteriorated.

What is the basic function of the Academy?

It is primarily a body of scientists with very few research institutions. We set up research units only if something is very new. The last one we set up was for ecological economy. We have a marine biology station, a solar observatory, and a few other research facilities. We used to have a space research institute, but we let the government take it over. We used to own the Museum of Natural History, but it is now part of the University of Stockholm. We started the Bureau of Statistics and also the Bureau of Meteorology and, again, they are now government organizations. We cannot afford to run these projects forever; we need our resources for new initiatives.

How would you characterize the prestige of the Swedish Academy?

One of the things I realized while I was President was that we have high prestige among the national academies. There are only a few that are better known, for example, the Royal Society and the National Academy of Sciences in the United States. Our prestige is mainly due to the Nobel Prizes. There is, however, an additional component. Sweden has been a neutral country and has not been a colonial power. During the Cold War era and in discussions between the industrialized nations and the Third World, Sweden has always been in between. When the academies of the Third World met in Kuwait in 1992, and there was a discussion of promoting science in the Third World, I was invited to be the chair. Our Academy has played a pivotal role in the world population discussions as well as in bringing together the organizations of all European academies. People have listened to us. We have pioneered environmental research and played an important role in getting the world together to discuss environmental issues.

How much, if any, politics was involved in awarding the 1995 Nobel Prize in Chemistry to atmospheric scientists?

None. There was no politics in it at all, whatsoever. We had discussed the research for which this prize was awarded for quite a number of years and found it very important, and it fell exactly within the statutes of the Nobel testament. This was thoroughly worked out by the Nobel Committee. No politics was involved.

Speaking about the Nobel Prize, do you tend to maintain, however loosely, some proportions between organic and inorganic chemistry, and so on?

No, not at all. There are no such considerations.

Nations, continents, age groups?

No, no, no. The only question asked is whether something is prizeworthy, and of course, we have the task of considering various suggestions. Everything is very carefully considered.

Did you ever study the history of previous prizes?

I did not personally study it. Everything is secret for 50 years. As of today, only the prizes for 1946 or earlier can be studied by historians. What

has been discussed lately is the prize to Otto Hahn and the question of why Lise Meitner was not included.

Do you have any comment on this?

No, I don't know anything about what happened at that time. I can only say that as a boy I heard a lot about Lise Meitner during the war. They talked a lot about her, and with enormous respect too, in our family. That is because I grew up in a family that was interested in the sciences.

How about gender bias?

I have been involved with the Nobel Committee only since 1992 so it would be very difficult for me to discuss anything about what had happened previously. I have never noticed any gender bias. I would like to say this though. There are many people who have been worthy of the Nobel Prize and never received it, but there is hardly anyone who received it who was not worthy. The prizes are too few, so there will always be people left out.

A lot of work goes into the evaluation. The cost of evaluating and giving out the Prize may be as much as the value of the prize, which is now about one million dollars. We have specialists who write reports. We send people abroad, and we bring scientists to Sweden who can help us in the evaluation.

It sounds like scientific research?

And it is indeed. It is also a hard decision, but, curiously, when it comes to the decision, there is great agreement among the members of the Committee.

Sweden is a relatively small country, and, obviously cannot pursue all directions in scientific research. How do you select the projects worthy of support?

A lot of it has to do with tradition. There are always some charismatic people with a vision around whom strong groups form. The subject of their research may propagate through several generations. For example, Linnaeus attracted so many pupils that systematic botany became one of the most studied subjects in Sweden. There were for a while more chairs

in systematic botany than in most other subjects, and it has taken a long time to get the right proportion. In the same way; Svedberg, Tiselius, and others introduced separation science as a widely studied field in Sweden. There is no central authority who determines a few selected areas worthy of special support, even if there have always been somè politicians who would attempt to make it happen. However, in the end, the individual scientists apply to the research councils for support, and their proposals have been judged on their quality alone, and not on their so-called "practical relevance." Scientists have been very much involved in the decision-making. They know that the best results are obtained when researchers are allowed to do what they want to do, and good scientists will always try to get, and will get, the recognition for their research.

What advice would you give for poor countries about basic research?

Not to pour money into something if they don't know what it is. At the same time, try to recognize charismatic scientists and support them. In Sweden we had the Linnaean tradition, and Linnaeus was a very charismatic person, and his line of research was propagated through generations into this century. I knew a woman scientist who, when she was 28, went to Cairo with her husband to study botany. Her husband died a few years later. He had been Professor of Botany, and she subsequently took over the Chair. She stayed at Cairo University for 50 years and wrote about the flora of Egypt. Many professors of botany in the Arab world today are her former pupils. Until a few years ago, botany was considered to be a science in decline, and now it is going up again due to molecular biology. I know her story because she was my aunt.

Please tell us about the Wenner-Gren Foundation.

It was started by the Swedish industrialist Axel Wenner-Gren. He made his fortune in vacuum cleaners and refrigerators. He founded the company Electrolux in the 1920s. He made a large donation in the 1950s to build the Wenner-Gren Center. It was opened in 1962 and consisted of several large buildings. Just before the recent fall on the real estate market, the Foundation sold its largest buildings for 650 million Swedish crowns. We are now using the earnings from this capital to support international scientific exchange. We send out about 50 postdocs annually and bring in guest scientists, about 60 per year. We organize international symposia

and support other projects. One of our projects is the Wenner-Gren Distinguished Lectureship. We have had two so far this year. You are the second, and the first was the President of the French Academy, Marianne Grunberg-Manago. I have a very interesting job here running the Foundation and dispersing 35 million crowns — between five and six million dollars — annually.

George Klein, 1999 (photograph by I. Hargittai).

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George Klein

George Klein (b. 1925 in Budapest, Hungary) is Research Group Leader of the Microbiology and Tumor Biology Center at the Karolinska Institute in Stockholm, Sweden. He started his professional career as Instructor in histology in 1945 and in pathology in 1946 at Budapest University. He was Research Fellow at the Karolinska Institute between 1947–1949. He received his MD from the Karolinska Institute in 1951 and has spent his professional career there. He was Professor of Tumor Biology and Head of Department of Tumor Biology until his retirement in 1993. In addition to shorter term visiting appointments in the United States, he was Visiting Professor of the Hadassah Medical School at The Hebrew University of Jerusalem between 1973–1993. He is a Member of the Royal Swedish Academy of Sciences, Foreign Associate of the National Academy of Sciences (Washington, DC), he was a Member of the Nobel Assembly of the Karolinska Institute between 1957–1993, he is a Member of the Academia Europaea, and many other learned societies. He is decorated with numerous awards from many different countries for his scientific research and has also received literature prizes for his increasing activities as an author. Some of his books have appeared in English, such as *The Atheist and the Holy City*, *Pietà* [MIT Press]; *Live Now* [Prometheus Books, Amherst, New York, 1997]. George Klein is a well-known personality in Sweden, not only as a scientist and writer but also because of his frequent participation in public dialogs and discussions. We recorded two conversations in Budapest, on October 2, 1999 and on September 2, 2000. First I asked George Klein to single out something from his research contributions.

I consider my most important scientific contribution an insight, not an experiment, that chromosomal translocations in tumors, that is, exchanges between two different chromosomes must reflect oncogene activation events. It was a sudden insight but it came from very unexpected observations. I had a very strange situation in my lab at one point. I had a Japanese–Hungarian group of mouse cytogeneticists who would have never touched a human tumor and I had a Bulgarian guest worker couple who worked with human chromosomes and who would never look at mouse karyotypes. The two groups didn't collaborate or even discuss, yet they discovered precisely analogous translocations in a mouse and in a human tumor whose only common denominator was that both originated from immunoglobulin producing B-lymphocytes. My insight came from the fact that the same terminal chromosome fragment was translocated to three alternative sites, located on those other chromosomes that carried the three immunoglobulin genes. I suggested that the common donor chromosome carried an oncogene that became activated by a juxtaposed mildly active immunoglobulin gene. Surprisingly, this turned out to be true through the work of others. I published the hypothesis in *Nature* in 1981. The confirmation came from four different labs, three in the U.S. and one in Australia in the following year.

Most of our experimental work was in tumor immunology. In the late 1960s and early 1970s, we were among the first to show that chemically and virally induced tumors could induce rejection responses in genetically identical mice and even in the original primary host. Earlier, at the end of the 1950s, we analyzed changes in experimental tumors that turned from an adherent cohesive form to a freely dissociated form of growth. We showed that this was due to variation and selection, which was a new idea then. This is what started to make our work known. In the beginning of the 1970s, we found with Henry Harris from Oxford that fusion of normal with malignant cells led to the suppression of malignancy. The opposite was expected because the malignant phenotype was believed to be dominant. This was the beginning of the tumor suppressor field.

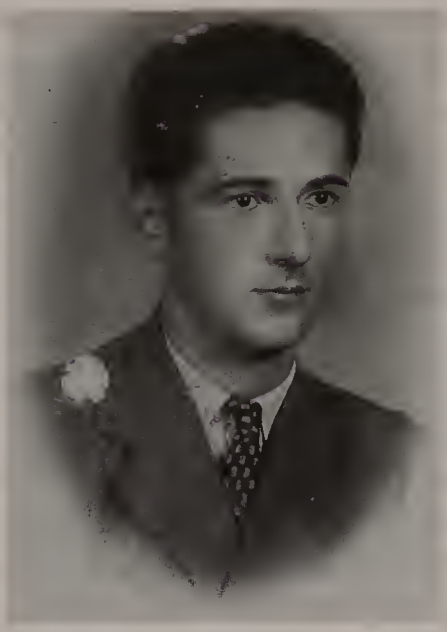
What was in Sweden that you created and what only you could have created?

It was not done intentionally. I did not even realize how important it was for the building up of my institution that I am not bound by some of the traditionally Swedish inhibitions. Four decades later I published a

book of correspondence with a former politician, Per Ahlmark. He used to be the leader of the Liberal Party and a former Deputy Prime Minister until he suddenly got fed up with politics and became a journalist and writer. He is very Swedish but he is also the greatest friend of Israel and the Jews in Sweden. He is an indefatigable fighter against Nazism and anti-Semitism. It was he who had initiated the legal process against a virulently anti-Semitic radio station in Stockholm, called Radio Islam. The title of our book is *Resistance* (*Motståndet* in Swedish). In my last published letter to him I write about "your Lutheran hell" and I mean the many guilt feelings and human interaction problems Swedes often struggle with. You keep watching yourself all the time, you are very conscious of your behavior, and you have a bad conscience most of the time. The ever-impending fear of making mistakes impedes your decisions, you often become stuck in small hesitations. Jewish culture is very different. Even though I am not much of a Jew, I am conditioned by Jewish attitudes. A good Lutheran listens carefully to the opinions of others, he has to or at least has to pretend that he does. He has to avoid talking about personal matters, opinions, anything that could hurt other peoples' feelings. This can be very useful for collaborations and for committee work. That's why their organizations function so well. At the same time people are often hesitant to put forward their own views and to choose their own direction. A Jew can be quite different. In contrast to the Lutheran who approaches his God through the priest or the religious community, the Jew talks to Him directly, even if he does not believe that he exists. This makes the Jews more spontaneous, colorful, and interesting, and often more intolerable. This is also explaining why it is more difficult for Jews to function in committees and other cooperative modules.

In Sweden, I got the possibility to develop my system in my own way. Once you get your own institution — and this happened to me at the age of 32 — you do what you want as long as you produce something and your unit functions peacefully and effectively. I did not do this alone. There were many other foreigners at the lab of Caspersson where I worked, especially Americans who are very good in informal communication and do not have the Swedish hesitations.

Another important factor was that there was virtually no experimental cancer research in Sweden when we started. Like in other developed countries of similar size, disciplines that were good in Sweden could be linked to individuals. The great tradition in biochemistry, for instance, is due entirely to a few individuals. Biochemistry is a good case in point. Areas without



The student George Klein (courtesy of George Klein).

a strong tradition could be quite provincial. The chance to develop cancer research in Sweden was quite good.

So nobody gave you a specific mandate to do this.

The mandate was my professorship. The professorial appointment is signed by the King and I still have it on the wall. It states that the King appoints me as Professor of Tumor Biology as of July 1, 1957, and my duties are going to be defined by the Chancellor of the universities. Those instructions have not yet arrived.

How far ahead do you plan what you want to do.

I don't. I never plan anything unless forced to. I used to tell my students that a plan is a grammatical fiction. I never hid my view on this from anybody. We tried to follow wherever the problem was leading us, plan or no plan.

What did you achieve organizationally?

It's all temporary. I always looked at my "organization" as a sea with moving ice on which you are trying to drive a truck. That's the way it should be in science, where everything is in continuous motion. Everything always depended on temporary grants.

Was there a competition for your professorship?

No. It was a personal professorship, requested by Karolinska and supported by the Swedish Cancer Society and the Medical Research Council. That was one of the last personal professorships in Sweden. Earlier, Theorell, Caspersson, Granit, and some others had personal professorships but by 1957, it was being phased out.

You mentioned that your friend waged a fight against anti-Semitism. Is there anti-Semitism in Sweden?

There are neo-Nazis in Sweden like everywhere in Europe. There was also the infamous case of Radio Islam. I was a witness of the prosecution. A well-known Professor of Theology in Uppsala, Jan Bergman, was a witness of the defense. Among other subjects, he was teaching Judaica to Swedish theology students in Uppsala. He said in the court that Radio Islam — a purely anti-Semitic station that was broadcasting the most vicious Nazi propaganda in Europe since the war, totally undisturbed, during two years — has made some good points about the Jewish religion, that was indeed a cruel religion. He also said that the statement that it was a mitzvah for a Jew to kill a non-Jew was correct. There were many other points like that. Later, when Bergman was criticized, the professors of theology in Uppsala came out almost unanimously in his defense. They regarded the debate as an attack on the Church. I was amazed to discover how much latent anti-Semitism existed in a faction of the Swedish Lutheran Church. It is the classical anti-Semitism built on the view of Jews as the murderers of Jesus, mixed with a certain amount of leftist radicalism. In the public debate that followed, the theologians, supported by some other professors, tried to sweep the issue of anti-Semitism under the carpet and pretended that they defended the right of free speech. At one point the University called a foreign expert to evaluate the theological debate. It was a former Rector of the University of Oslo, a well-known and much respected theologian. He wrote a long and very strong statement. He found it totally unacceptable that the theologians of Uppsala University tried to fight criticism by focusing on minor inaccuracies without entering a serious discussion of the major issue, anti-Semitism.

Ahlmark has been a tireless fighter against anti-Semitism and also against the distortions of the New Left in this and other matters. In the wake of the student unrest of 1968, and the strong campaign against the Vietnam War, it was very difficult to write anything about what was going on in

the Soviet Union and in the satellite countries. Whoever tried to do anything about it was simply forced out. Ahlmark has now written several well-documented books about this of which *The Open Wound* is the strongest. More and more people see that Ahlmark was right.

How did you become a writer?

My first book was published in 1984. Fifteen years earlier I met a Swedish publisher at a dinner party. A few days later I received a letter from him, asking me to write a book. This surprised me very much. After some pondering I responded that I had nothing to write about that would interest other people, I had no language in which to write, and I had no time. A decade later, I had one of these intelligent and inquisitive Israeli students at the lab, who, unlike the Swedish students, are very curious. I told him about my encounter with the publisher. The student said that I should write a book. So I asked him to compile a table of contents for my first book by tomorrow, and I would write something if his table of contents would amuse me. Next day he presented me with a list of contents, which was essentially an autobiography — Budapest, Stockholm, Jerusalem. This was the time when our regular visits to Jerusalem started. Since I found his suggestion amusing, I started dictating a text into a dictaphone. It was easy because I could do it while driving a car or standing in line. I found it stimulating, it took away the boredom of routines. I dictated my story as I remembered it from the age 3 to 22, when I went to Stockholm. I sent it to the publisher. He wanted to publish it but he also wanted me to add two more parts, one about what happened to me after my arrival in Sweden, and another part about science. So I did. It became an autobiography, entitled *I stället för hemland*, which means "instead of a homeland." Writing that book was a pleasurable experience for me. Normally, even today, when I do this, I do it with a guilt feeling because this is not really my job. I rationalized it, however, by saying that it was helping my real job and, actually, it did. It surprised me, when the book was published, that people read it, there were reviews, and I was invited to discuss it. The next thing was that I received a book in German from another publisher who asked me to write a Preface to the Swedish translation. It was entitled *Diktate über Sterben und Tod* ("Dictations about Dying and Death"). It was written by a Swiss Professor of Criminal Law, Peter Noll, who received a cancer diagnosis, at the height of his intellectual and physical prowess, in his early fifties. After looking into his prospects of a good life, he came to the

conclusion that even if the operation would succeed, he would be "in the hands of the medical industry," and, in his own judgement, an invalid. This was not compatible with his own perception of life and death. Therefore, he refused every form of treatment. He had nine months to live and dictated the book during that time. I did not think I was interested in this book but when I glanced into it, it caught me totally. I wrote the Preface that became an essay, and that became the nucleus of further essays. Everything happened by chance and by following my own attractions and repulsions. This is still the case. Unless it gives me pleasure, I cannot do it.

Do you think your writings will be more important in the long run than your research?

I never think in those terms. I never assess the "importance" of what I am doing. I have a strong aversion against trying to assess the impression my person or my activities make on the superficial observer. When I speak to a lady and I notice that she looks at how I am dressed — and ladies do this all the time — I dislike her in that very moment. If somebody tells me, after a talk, that I looked well, that I spoke well, etc. I just hate that. I want to know peoples' reactions to what I said.

I was often trying to determine the source of my driving force. So I would like to tell you about a moment when I discovered one part of my driving force, fully realizing that it is more complex. As you know, Midsummer Night is an important event in Sweden. During a decade, 1965–1975, we received tumor material from Africa every week. On one occasion, the plane came on the day of Midsummer Night. The normal routine was that the staff came in late afternoon after the material arrived, they worked overnight and had the next day off. This time I could not ask the staff, all girls, from going out and dance. I told them that I would do the experiments myself. They gave me a crash course in what I had to do and off they went. The material arrived, it was of excellent quality. I found out soon enough that I was not doing well and although I tried to do all kinds of panicking things, when I was looking in the microscope at dawn, it was clear that I'd destroyed everything. And yet I felt very happy. When I tried to find the source of my happiness, I realized that I felt elated because I didn't have to go to the dance. There is thus an element of escapism in my motivation. It comes from much earlier times. Even in my early teenage years I always wanted to escape from most social contexts. Therefore, I look at what I do as small waves on the surface

of water and very few things are really important. Shakespeare was important and so was Dante, and they even may not have thought so. Whether something is important or not is of no concern to me. I have great difficulties in understanding the concern of my colleagues about this kind of prestige and I find the endless worry of some of them quite boring.

There are legends about how careful you are with your time. Can your time management be explained with this escapism?

It can. What drives me basically is the fear of being bored, which means mental inactivity. This is characteristic for ambitious, assimilated Hungarian Jews and, *mutatis mutandis*, it could be a heritage from the Orthodox. In Sweden, it is considered unique, or less politely, silly. It must have its basis in discrimination and reactions to it. Szilard, Teller, von Neumann, Wigner, Paul Erdös and other great Hungarian Jews are but a few of the many outstanding examples. There are thousands of less or not at all outstanding examples where the drive runs empty, but it is still the same drive. The moment your brain is not active, depression or anxiety enters. For me shaving is a low point because I am losing mental activity. People think that this is all done in order to be efficient, oriented towards success, to achieve and produce maximally. I get a lot of advice, "Relax, have a good time." But what is a good time? The very word "vacation" gives me chills.

For many the ultimate goal and success is the Nobel Prize.

Having served for decades on the Nobel Committee, I call that disease *Nobelitis* (and there is another one also, *Nobelomania*). *Nobelitis* is the disease of those who are close to the Prize, or think that they are, but do not get it. They may become very disappointed and unhappy. By the way it is interesting to follow what happens to people after they receive the prize. Some are destroyed by it. Others continue as before. Those are the real scientists who never had *Nobelitis*. Monod used to say, "The Prize is very good for science and very bad for the scientists." When our Professor Göran Liljestrand retired after having served as secretary of the Nobel Committee for Physiology or Medicine for 35 years, a journalist asked him about the positive and negative effects of the Nobel Prize. He saw no aspect of the Prize that would not have both positive and negative effects. Hard pressed by the journalist to find one that has only positive effects, he replied that there was one, but only one. It forced the professors of Karolinska Institute to read some literature.

The young researcher George Klein (sitting in center) among colleagues at the Karolinska Institute in Stockholm (courtesy of George Klein).

You have explained the anxiety and the origin of your anxiety and if we can return to it, wasn't more than 50 years living in Sweden for you enough to repel it?

No, it wasn't because its origin is older and deeper than my brief existence. It has clearly a genetic component. This is what we have been selected for over the centuries in the ghettos. Jewish boys with a reading head could cross the barriers of poverty and marry the beautiful daughter of the rich man. The rich man may not have been an intellectual but he had practical talent. Jews always had a high regard for learning and the rich man was happy to give away his daughter to a bright student without a penny. There were also important environmental factors. We here in Budapest, and by we I mean the middle-class Jews with this kind of tradition, got the drive and the ambition with mother's milk. You either became successful or you were going to end up in the gutter. We did not see anything between these extremes.

But if there is a genetic component, say, in the large number of American Nobel laureates of Central and Eastern European Jewish origin, it seems

to disappear in a few generations down the line, not to speak about the lacking Israeli Nobel laureates.

I have been asked this question in Israel many times. Why are there so many Jewish Nobel laureates but not a single Israeli scientist among them? My answer is always two words in Hebrew: "Atem babait," which means, "You are at home." A Jewish professor at Harvard feels that he has to run ten times as fast as a non-Jewish professor in order to convince himself that he is still standing in the same spot. That particular drive is not present in Israel.

You've had a tremendous career. Hypothetically, had you stayed in Hungary ...

It would've been zero. Let me illuminate my answer with an example from a later time and from Sweden. In 1966, I had a very unpleasant situation in Stockholm, after having had a very pleasant situation. Suddenly everything just blew up around me. At that point I got an extremely attractive offer from Harvard. I would become Professor of Genetics with excellent working facilities, and the students there are extraordinary as you know. For six months I thought that we were going and then, one day, I suddenly realized that we were not going. I had to admit to myself that I never wanted to go, that I was playing for the galleries, and that I was only fooling myself and everybody else around me. While I don't fully understand all facets of my decision, an important component of it was the realization that in Sweden you don't have to be a good member of the society, you do not have to be a good neighbor, you don't have to do all the social things. But in America, you have to. I realized that being urged to do that and whether I resisted it or not, I might easily become a dysharmonic and unhappy person. In Sweden they may laugh at some of my strange behavior. They may be unhappy when I run away from a dinner party or do not come, but they accept it because in Sweden your privacy is respected. In America, there is a stronger pressure to conform. In Hungary, there would've been all the political problems compounded with the much more severe pressure to conform. I would've never survived that. In the Fall of 1944, I was hiding in Zugló. One of my distant relatives was an illegal Communist. As soon as we came up from the cellar in January 1945, he took me to a meeting with other Communists. All the way to the meeting he was giving his wife instructions how to behave, what to say and what not to say. It was clear that all the decisions came from

above, ultimately from Moscow. I did not want to have anything to do with Communists after that. It was not only the politics about which I could not yet have formed a clear opinion. It was the pressure associated with being a member of a closely-knit society that repelled me. I could not stand the idea that others should decide what I should be thinking and doing. This is a crucial question for me. I already had this notion at the age of 12. Being fatherless may have something to do with this, the fact that you're not expecting a father figure to make decisions for you.

May it be that part of your popularity in Sweden comes from a combination of your being a Holocaust survivor and a Swedish guilt for Sweden's role during World War II, and may it also be that part of your popularity originates from the Swedes looking at you as a curiosity?

The Holocaust is neither here nor there in this respect. When I came to Sweden in 1947, nobody wanted to hear what had happened. The same was true during at least twenty years after that. Now it is the opposite. Now there's an enormous interest. But that is due to a single man, the present Prime Minister, Göran Persson. The previous Prime Ministers couldn't care less. Ten years ago we had the most vicious anti-Semitic propaganda in Sweden through that radio station I had mentioned. It went on for two years before legal action was taken, and the Prime Minister was totally uninterested. Today, there is a large program called "Living History," which is centered on the Holocaust, and the present Prime Minister started it.

Does it mean that Swedish public opinion can be influenced so strongly by just one person, in either direction?

Yes. The Swedes have always been extremely obedient and they still look for normative directions from above. They still have the old Lutheran system at the basis of the secular society. In the old days there was always conformity within the parish. Part of the people who immigrated to America did so because they couldn't stand it.

How can such a system be so accommodating for you?

Because they leave you alone, it is part of their very deeply founded respect for privacy and freedom of opinions. If you are not in a Swedish family, you think what you want. In some respects Sweden is the opposite of Hungary. Hungarians have been quite tolerant in questions of behavior

but less so when it comes to opinions. In Sweden there is absolute tolerance for opinions but little tolerance of deviating behavior. One of the elements of good behavior is that you're a good member of the community and you look for normative principles. But, of course, I am outside this community and that is accepted.

There are people in Sweden who like me and people who hate me. Probably more people like me than hate me. Among colleagues one reason may be that the academic structure means very little for me. My transition from student to professor was not accompanied by any change in relation to the customary formalities of behavior. In the same way, I couldn't care less about what the title of somebody is. I am a member of various societies and academies but I never go there. I stand away from what I call the monkey play, the social interactions driven by who is what. Our lab was always non-hierarchical, non-ethnicist, non-racist, and non-sexist. One of my female doctoral students said 25 years ago that I should be an honorary president of a feminist emancipation organization because I had never shown the slightest tendency for sex discrimination. The truth is, however, that the sex of a person is as immaterial for judging the work as the color of the hair or the eyes.

Maybe some of the Hungarian Jewish attitudes have a selective advantage in this academic society. An example involves Olivecrona, the great brain surgeon, whom you know from Frigyes Karinthy's book. When Olivecrona was retiring, they were looking for his successor. According to the law of the time that has been changed since, nothing else could be considered even for a clinical professorship than the originality of the candidate's scientific research. The ability to perform operations was irrelevant. In this case, the faculty could not decide on the choice for two years. They finally selected a person who was an outstanding scientist but has not operated for years because he was the best scientist. He had to be appointed. It would have been against the law to pay attention to the fact that he has not operated for 20 years. He was appointed and after a year or two the clinic was collapsing. Although the new chief did not operate, the operations were carried out under his name because he was the boss. Qualified staff left, one doctor committed suicide, and an entire section was closed. It was becoming a public scandal. Suddenly, Laszlo Steiner came along, a brilliant brain surgeon, a Hungarian Jew from Romania. He managed to escape through Berlin just before the Berlin Wall was erected. He got a job as an Assistant Professor. He took over the supervision of the operations, he worked day and night and didn't care that he wasn't the professor.

He let the professor have all the prestige he wanted to have. He couldn't care less, he just wanted to operate. He is a tiny frail man who can sit and operate under the microscope for 8 or 9 hours. He is an expert on the fine vascular surgery of the brain. The staff around him must be taking shifts because nobody can endure that long. Ten years ago he reached the age 65. He had to retire and never touch another patient in Stockholm. But then he became the head of a large neuro-surgical clinic in Charlottesville in the United States. He just carries on as before because for him the most important thing is to do what he was doing; that is his drive. We do have this in us for reasons that I had mentioned before. I'm not saying we have this for great moral reasons. We have it in us because that's the way we have always survived as ghetto Jews. That's what matters to us and not the hierarchy.

The Swedes sense this. They don't articulate it, maybe they are not conscious about it but they like it. They see that I'm different and I do not have some of their common ambitions. Sometimes they come to see me in private and pour out their soul, something they would not do with other Swedes. They do not want to show their weakness to the others but they feel they can show it to me.

You mentioned feminism. Your wife, Eva, is a member of the Royal Swedish Academy of Sciences, a very rare distinction. Has this ever intimidated you in any way?

No, nothing could be more removed from me. My mother was a wonderful housewife and was very concerned that I am well fed and well clothed. She was overprotective as Jewish mothers often are. My father died when I was one year old. When I was a young child I had this desperate wish to talk to her. However, every time I started a conversation with her, very soon I would see in her look the worry whether I was properly dressed, whether I was not cold, whether I should perhaps eat something more. This turned me off from housewives forever. I deeply loved my mother but there was this barrier between us, which could never be overcome, because she never really understood the problem. I could therefore never think of marrying somebody who was not an intellectual person. For me it is very hard to understand men who do not want an intelligent wife.

We have had various conversations about human behavior under various conditions and this question seems to interest you a great deal.

Eva and George Klein, Stockholm, 1997 (photograph by I. Hargittai).

It is important to realize that you cannot judge how you will behave under severe stress. In the early 1950s, at the very beginning of the Stalinist era in Hungary, a bacteriologist, Professor Farago was accused of having contaminated purposefully a Pertussis vaccine with living bacteria and caused several children's death. Farago was imprisoned where he committed suicide. Of course, the accusation was nonsense, it was an accidental contamination. He and his assistants could've been persecuted for carelessness but they accused him with having done it on purpose to sabotage the system. One of his young doctors, József Sinkovics was also in prison for more than a year. They tortured him because they wanted him to sign a statement to assert that Farago had been conspiring. Sinkovics set up a scheme for himself. If they kick out his ribs, which they did, he would not sign; if they knock out his teeth, which they also did, he would not sign. If they would kick his genitals, he would sign. If they would bring in his mother and torture her in front of him, he would also sign. Fortunately, it never came to these points and he never signed. I know Sinkovics well, he is an outstanding virologist in the U.S. and I believe him. But even this story is a construction for our present discussion because unless you find yourself in a real situation, you never know. Sometimes you do better than you would've thought and sometimes you do worse.

We have spoken earlier about Germany and how to judge Germans with respect to the Holocaust. I would like to stress that the proportion of the hard-core anti-Semites in Germany, before Hitler, was similar to other European countries like France and was probably lower than in Poland

and Russia. The Holocaust happened because of the coincidence of several unlikely events. The first was that a paranoid anti-Semite who truly believed that the Jews were striving for world domination and that they caused most of the ills of humanity attained supreme power in a strong country. Such people always existed, and always will, but the likelihood that they reach supreme power in a strong nation is very low. Yet that has happened. The second improbability was his extraordinary talent to incite the masses to follow him. We only hear the hoarse shouting of Hitler's speeches and fail to understand his influence but professional rhetoricians say that they are masterpieces of rhetoric. They always start in a very low key, and intensify gradually, playing on the desires, hatreds, and frustrations of the people. They manipulate the feelings of the audience until they are carried along. In the end, they are ready to follow him blindly. Nobody in Hitler's entourage had a similar rhetoric ability. The third component was the traditional obedience of the Germans to the State.

Today's young Germans find the deeds of Nazi Germany just as repelling as anybody could. The Germans have done more soul searching than the Japanese who have barely faced their own past and the atrocities the Japanese had committed during the war. Take the Swedes. My friend, Bosse Lindquist, is an investigative journalist. He was the first to ring the alarm bell about the Swedish sterilization program. He wrote a book entitled *Förädlade svenskar* ("Ennobled Swedes"). He showed how active some of the founding fathers of Swedish Social Democracy were in establishing a strong and discriminative Swedish sterilization program.

Lindquist recently went to Cambodia and visited the areas of the Khmer Rouge. He interviewed several of their leaders who had participated in the Pol Pot massacres. He also interviewed the Swedish diplomats who were the first westerners allowed to visit Pol Pot's Cambodia. In their wake came Swedish writers and journalists, including pro-Vietnam, anti-American movement leaders, among them the present Speaker of the Parliament. They came back, while the massacres were going on, with glowing reports of a fantastic revolution. They maintained that all the talk about atrocities was hostile propaganda. They essentially endorsed Pol Pot. They had great influence because the world did not know what was going on, and they were respectable Swedes.

Now the former Khmer Rouge leaders told Lindquist that they have made a show because they knew that the Swedes would believe anything. They extra fed some people, they gave them extra clothing for the duration of the visit, and cleaned up the regions the Swedes would visit. Lindquist

has questioned some of the former Swedish diplomats about these visits. One of them said that an ambassador owes his first loyalty to his government. Their instructions came from Stockholm. It was the time when the pro-Vietnam movement was very important in Sweden. It rallied the youth against America. It was the time of Olof Palme. Elections were approaching and the instructions were not to do anything that would disturb the elections. They were told not to cast any shade of doubt on the policies of the Palme government.

You are saying the most terrible things, very disturbing.

I hope so, because we should be aware of this, not to distribute blame, but to be frank about the ways we function.

How do you feel about the difference between Sweden and Switzerland looking back to World War II?

It's very different because at that time Sweden was only geographically a peninsula, it was really an island. It was not in the middle of Europe, it was not interested in what was going on in Europe. Switzerland was in the middle of everything. Sweden did not do so badly with the refugees and helping the Norwegian resistance. Had they not permitted the Germans to use Swedish railways, Sweden would have been occupied. The Swedish iron ore was one of the most important resources for the Germans. Sweden has always been selling that iron ore to Germany and in order for them to stop that would have meant breaking with a long-standing practice. If you ask the Norwegians, would it have been better if Sweden had also been occupied by the Germans, they would say, certainly not. For Norway it was very good to have this hinterland all the time. It's not an easy thing to judge. Switzerland has always been xenophobic. They are also xenophobic towards the other Swiss citizens who belong to the other Cantons. It is the provincial local patriotism of the mountain peasant.

You must read a tremendous amount for your research and for your writings. But when the day is over, what do you read before you go to sleep?

I read Hebrew as my means of falling asleep every evening. That's why I know several Israeli writers because I keep reading their novels. This is my universal method of going to sleep. I need a text, which is exciting,

so I look forward to reading it in bed. It has to be a text that I can surf, so I don't have to understand every word to look it up in the dictionary. Since I don't have quick reading in Hebrew, I read slowly like a child until I suddenly fall asleep. I tried to read other things because I realize that it is very one-sided reading only Hebrew literature in bed, but whenever I do that I cannot sleep fine.

Back when Jim Watson's book The Double Helix *was still* Honest Jim *in manuscript, he sent it to you and you were one of the few who recognized it at once as a masterpiece.*

That's right. Sydney Brenner wrote me that I should be very proud of that letter. My letter was more than that I liked the book; I also predicted its future.

Watson never answers letters and he never answered my three-page letter either. I was very frank in that letter. Of course, we have met many times over the years but it was always about concrete matters. The first time I felt that he had a positive attitude about me was when a few weeks ago you wrote to me about your conversation with him. At that point I sent him one of my books. He immediately sent me back his new book with a very warm letter. So, here again, you see how accidental events shape things.

Watson is a tremendously lonely person. When he sent me *Honest Jim*, it was after I had visited him in his home and we had lunch with his father. Then while his father was watching baseball, Jim took me upstairs to his huge room, which was extremely untidy. There were wonderful records lying around, most of them Bach, and a lot of art, real good art. I suddenly sensed his loneliness among the paintings and among the Bachs. When I was then reading his manuscript, I found it very moving when he describes his trip to Paris, after the discovery of the double helix to celebrate his sister's birthday. When he walks down the Champs Elisée he knows that the Nobel Prize is his, but all those long-haired girls belong to someone else.

I read recently about a meeting of Watson with students in Oxford where someone asked him whether there would be a discovery in the 21st century, comparable in importance to the discovery of the double helix. Watson thought long and hard and finally said that probably there would not be such a thing. He may be right. I would've thought that he would say something about the nervous system because previously he was very enthusiastic about it. Maybe there won't be anything comparable.

You wrote a beautiful piece about Carleton Gajdusek and not only about his science but also as a human being and about his life philosophy. I have also experienced his engaging personality but he had been accused of pedophilia and that made him very controversial. Would you care to add anything to what you had written about him?

When I wrote about him, years before his trial, I may have been very naïve but I did not suspect that he was pedophilic. I accepted that he had enormous interest in people and in children in particular. He is a pediatrician, he has an enormous amount of knowledge about the development of the human mind. He never does anything without dedicating himself to what he is doing completely. I used his diaries in my essay. There is this particular scene about the dance when he is sitting alone, hoping that there would be one person coming along. I found a lot of similarity between him and myself except that in a similar situation I was hoping that a girl would come along and he was hoping that a boy would come along. This is but a small technical difference. The basic yearning to escape from the crowd and to form deep friendships with individual human beings is the same. I realized that he found an emotional satisfaction in those faraway places. I raised the question whether he sought these regions for that reason and his fantastic scientific achievements were a byproduct or it was the other way around.

In the New Guinea cultures that he was seeking, relations between teenagers of opposite sex would be unthinkable. The boys live together and engage in sexual play. This transforms into normal heterosexual activity, when they get married. In jail, Carleton wrote thousands of pages about what he considers as natural, playful sexual behavior. To him the villains are the Jewish-Christian-Moslem fundamentalists who introduced all the taboos on sex, to avoid uncertainty about paternity and in the interest of the patriarchal tradition for properly dividing the land. He sees this as a perversion of normal human sexuality that should be relaxed and non-neurotic. He tried to establish the same culture in America that others could emulate. This is immensely naïve, and he was sentenced for that.

I hated the hypocrisy about sexuality when I was growing up here in Hungary. My schoolmates took me to a whorehouse in Budapest when I was 17. I remember the place and address exactly. We were sitting in the waiting room, waiting for the girls to become available. Because we were so young we were given discounts. Then suddenly the lights went out and some older gentlemen were leaving the house. The madam then

told us that she turned off the light because she didn't want any of us to see our fathers there.

I love children and I am very worried about their development. I know what immense damage one can do not just with sex but with all kinds of things, words, for instance. Any pedophiliac who damages children has my unqualified hatred and unforgiveness. In Carleton I don't see that. I have seen the innumerable letters that the boys sent him to jail, calling him their father and their brother. Many of them are now grown-ups and had called their own children Carleton or Gajdusek. I saw these boys around him, I saw them in their house, I know that he had spent his last penny on them and particularly on their education.

Swedish science benefits a lot from awarding the Nobel Prizes.

Sweden benefits. As everything, this is also double-edged. At the Karolinska, we have the most incredible series of seminars. Many of the best scientists in the world come to give talks. They think they have to show themselves. The students go to the seminars and think that this is the routine everywhere. And when they hear compliments about the Karolinska, some of which are quite exaggerated, they may be misled to think that the visitors come because we are so outstanding here. This is extremely dangerous.

Given the influence of politics on Swedish diplomats and even journalists, is it unimaginable that members of the Nobel Committees would also fall, even if to a minor extent, under some political bias?

It's totally unthinkable. The scientists are not affected by politics, the scientists couldn't care less about the ideology. It is so unthinkable that this story comes to my mind. It is in a country whose name I forget, but the chief rabbi and the catholic cardinal are having dinner together in the cardinal's home and the rabbi refuses to eat non-Kosher food. The cardinal is trying to convince the rabbi that it tastes so good. Finally the rabbi gives in and says, "All right, I will eat it some time later." "When?" asks the cardinal. "At your wedding," the rabbi answers.

Of course, if we consider politics in a very broad sense, for example to judge the relative importance of various fields, in that sense, there may be fierce differences in the opinions of various members of the Nobel Committees. Take the importance of the environment, for example, which I don't call a political question. One might think that the Nobel Committee or some of its members might wish to put a premium on what they consider important

George Klein receiving an award from President Jimmy Carter (courtesy of George Klein).

questions of the environment. Caring for and protecting the environment is a very Swedish thing. Or take medicine where some of the clinical professors feel that a discovery or invention of best practical significance in medicine should weigh more heavily than an important biological discovery. But it does not work because only pure science can convince the voting majority. (According to the rules formulated by Alfred Nobel, voting is by secret ballot.) By tradition, the members want to give the Prize to a scientific discovery that made a paradigmatic change.

Historical studies can now be conducted on the early Nobel Prizes. Analysis of the early physics prizes showed that those fields were strongly represented among the awards that were strong in Sweden at that time. I don't call that politics; that's the way things work. Everybody is for what he understands best, and everybody works for what he thinks is the most important. How could it be otherwise?

What people don't always realize is that the decision comes from a democratic procedure based on voting. Individual members have to be convinced. There are two reasons why the Nobel Prize, in my opinion, has achieved the prestige it has. One reason is that it is not open for

lobbying. The second reason is that in a Nobel Committee every professor is representing himself and his discipline. By tradition, everybody is motivated by the wish to give a good prize. A good prize is what everybody is proud of, it is for a discovery that has changed the world. This sort of thing can probably only materialize in a relatively small country, not in large countries where the pressure and influences can be much more profound. There must be a strong tradition of democracy, a tradition of law that governs the people. Not the State, but the Law. In this there is an enormous difference if you compare, say, Germany with Sweden. In Germany the State can be above the Law by historical tradition. In the Scandinavian countries, the Law is above the State.

There is a lot of misconception about the Nobel Prize. There is a lot of information that is available, but does not reach most scientists.

Even if it would reach them, they wouldn't believe it. People who know human behavior find such information counterintuitive. I have an essay, in Swedish, about the development of societies, the evolution of cancer, and the Korean plane. The Korean plane, 007, was shot down in 1983 by the Soviets. There was an investigation and a detailed technical report whose summary appeared in *The New Yorker* in December 1993. It documented a series of coincidences that were all very unlikely to happen but where each coincidence opened the way to the next one. Unless you know all this, you cannot possibly guess. People always try to make single causal connections, political connections, conspiratorial connections, espionage connections, which are all nonsense.

What is the lesson?

The lesson is that you either have the information to analyze a series of events or you don't. And if you don't, you better wait with your generalization. Cancer is a similar series of unlikely events. I compare this also with the development of society. Some Swedes were greatly puzzled by this comparison because they tend to believe that the development of society is a series of rational, planned events, which it is not. We now know, for instance, what an enormous influence a single person can have.

You said there is no lobbying for the Nobel Prize.

That doesn't mean that people do not try, but if there is any effect, it is the opposite effect. Obvious lobbying makes people very irritated. Of

course, lobbying may be done in a very intelligent way and we both know such cases, but I would say if someone has gotten the Nobel Prize after extensive lobbying, that person may have gotten the prize in spite of lobbying and not because of it. If somebody deserves the Prize, even lobbying for the Prize won't bar him from getting it. Otherwise, you should never analyze the awarding the Nobel Prize as a rational procedure, it is a race, a question of who gets ahead of whom, and lots of different human factors. You shouldn't be using rigorous causality in judging these things but introduce consideration of chaos as well.

As I have said, a danger of the Nobel Prize for Swedish science is that some people in Sweden may have the misconception that we are so much respected and we get the best scientists willingly coming to give seminars in Sweden because Swedish science is so good. This is extremely dangerous. It is just like the fact that Sweden was not in World War II. Many Swedes believe that this was due to the great political skill of the Swedes or the strength of the Swedish army. They may also think that Sweden, along with Switzerland, was ahead of the rest of Europe after World War II, because they worked better and harder. But the years went by and the destroyed countries were making fast progress and took over Sweden very rapidly. It is so easy to become conceited. We first visited Norway in the 1950s. As soon as people found out that we were not real Swedes, they became much friendlier. The argument that irritated them the most was when the Swedes boasted that the Germans did not attack them during World War II because they were afraid of the Swedish army.

Are you a crusader for anything?

Yes, for one thing, to persuade people to stop smoking. It is the single most important cause of cancer. It's an incredible absurdity that this was known already in the 1950s. I feel like Howard M. Temin (1934–1994), who was one of the most brilliant cancer researchers. (He shared the Nobel Prize in 1975 with Baltimore and Dulbecco "for their discoveries concerning the interaction between tumor viruses and the genetic material of the cell.") Temin was an original thinker who predicted his discovery ten years before he made it, and nobody believed him. He was very consistent in answering the journalists' questions about his work, "If I am going to tell you about my work that led to the Nobel Prize, you'll stop listening within one minute. You will not be so interested that you will pay any attention to what I am saying. It has no practical significance. But you can contribute

to fighting cancer in the most significant way. Just write that people should stop smoking, because it is the most important cause of human cancer." Temin was right. The tobacco companies spend more on advertising than the total NIH budget. The tobacco industry conducts a sophisticated and psychologically clever advertising campaign to recruit the youth. It amazes me that the same people who pay great attention to small amounts of radioactivity in the environment, causing perhaps one case of leukemia per year, may be chain smoking at the same time.

Do you have heroes?

Many.

Can you single out any?

No. I have too many heroes. Most of them are writers, composers, artists, not scientists. I have an almost superhuman adulation for Rilke. I just finished a hundred page essay about Imre Madách and his *Tragedy of Man*. The essence is that all ideologies are doomed to death, they are all hollow inside. Life survives, expressed in the prégnancy of Eve; it always wins and ideologies lose. Madách has been attacked from all sides, including the Church and the Marxists philosophers. Madách is one of my heroes. Some giants of Hungarian literature called him the most important generator of ideas. Of course, the idea that he presents is not pleasant. It depends on who your hero is. If you still look at God as the most important person in the *Tragedy* rather than the senile old man he appears in my reading, you have a different picture. I consider Lucifer a great skeptic philosopher and the hero of the *Tragedy*.

I also have a few scientific heroes but definitely fewer than writers. Temin is a good example. He got the right idea and he didn't know how to prove it because the technology was not there. Then he started experimenting in a very poor way, unconvincingly while nobody believed him. He suggested that RNA tumor viruses make a DNA copy. It was against everything at the time. Then he developed the technology during a decade and showed that the idea was correct. Independently, David Baltimore, an excellent biochemist, did the same experiment and proved the same thing at the same time. It impresses me that somebody can go on working in spite of total skepticism. I also admire Avery and his team coming up with DNA as the hereditary material when everybody else believed that only the proteins could carry information.

If you were to interview George Klein, what would you ask of him?

Wow. This is your first really difficult question. But, of course, it's a non-question because what I would ask him if I were not George Klein, would be determined by who I am and since I am George Klein, your question is impossible.

What would it be if George Klein would be interviewing George Klein?

This is what I am doing all the time because you are asking me a question and I digress in hundreds of directions.

You are now 74 and you are extremely fit and you feel very fit too. But just hypothetically, what is what you find important to leave behind when the time comes?

I am very interested in the question of death and dying, and attitudes to death, I have been ever since I wrote that Preface to Peter Noll's book. I visited a hospice in London. I asked the doctor in charge who was about 35, a stupid question, comparable to when people ask me "When is the riddle of cancer going to be solved?" My question to him was, "How can you cope with it?" It was a stupid question because he would not be there if he couldn't cope with it. Actually, he loved it. He showed me around and I understood what he was doing. The people they admit have about one month to live. When they come in they are told, "Yes, you are going to die now, and we will do everything we can to make it as painless as possible. But you are not going to die today. Therefore you have a day, today. Tomorrow, you will probably not die either. So think about what you would like to do today and tomorrow. It's amazing how this brings people, who had been sitting in the waiting room of death for months, to life. They think of things to do. One wants to see somebody, another wants to arrange something, financial or other. An old lady discovered that two student nurses had never been to Covent Garden. She bought tickets for them and went to see a ballet with them two weeks before she died. What I'm trying to say is the same idea that had been put forward a long time ago by Montaigne and before him by Seneca. This is also what Peter Noll's book is about. The awareness of death enhances your feeling for life. You cannot have a deep feeling for the intensity of life unless you are aware of the vicinity of death. Peter Noll, who had a very limited period of time to live, because he did not accept treatment,

knew that his time was limited. So is the time of everybody else but we, who don't know when we will die, are behaving as if we would be immortal. What do you want to achieve before you die? This question is related to the illusion of immortality. Noll is very critical on that point of himself. He asks himself, Why am I writing this book? Am I writing it to survive a little longer? Then I will destroy it. Am I writing it in order to get some affection? If so, I shall destroy it. But he goes on writing it to transmit an important message. Awareness of death gives us a feeling for life and the fullness of everything today. I think that this is the only thing that matters.

D. Carleton Gajdusek, 1999 (photograph by I. Hargittai).

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D. Carleton Gajdusek

D. Carleton Gajdusek (b. 1923 in Yonkers, New York) was co-recipient of the Nobel Prize in Physiology or Medicine in 1976 with Baruch S. Blumberg "for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases." Gajdusek studied always-fatal subacute diseases of the nervous system including the disease called kuru in communities of stone-age culture in New Guinea. He showed that kuru was transmissible and caused by a new type of infectious agent spread through cannibalism of their dead relatives. He further showed that this agent was closely related to that causing scrapie in sheep and that a rare worldwide pre-senile dementia, Creutzfeldt-Jakob Disease, was caused by the same atypical, unconventional "virus," and bovine spongiform encephalopathy ("mad cow disease") is caused also by one of this group of agents.

Gajdusek studied at the University of Rochester from 1940 to 1943; he took physics, mathematics, chemistry, biology, and embryology, among others. Between the ages of 19 and 22, he was at the Harvard Medical School and earned his MD and at 26 years of age he had qualified as a specialist in clinical pediatrics. At the ages of 25 and 26, he did postdoctoral work at the California Institute of Technology with Linus Pauling, John Kirkwood, and Max Delbrück. Following a series of clinical experience, Gajdusek was drafted in 1951 to Walter Reed Army Medical Service Graduate School. In 1957, he joined the National Institutes of Health where he directed a unit called Study of Child Growth and Development and Disease Patterns in Primitive Cultures and the Laboratory of Slow, Latent and Temperate Virus Infections and for 30 years the Laboratory of CNS Studies. In his research he spent extended

periods of time in remote areas of the world, including Iran, Afghanistan, Turkey, South East Asia, China, Siberia, South America, Australia, Papua New Guinea and other parts of Melanesia, Micronesia and Polynesia. He adopted, brought to his home in the United States, and educated over sixty children from Stone Age Cultures of New Guinea and Micronesia. Currently Dr. Gajdusek lives in Europe after having gone through a painful period of time back in the United States, which included arrest and prison term on charges of molestation and fiscal irregularities. A tremendous show of loyalty by his adopted children and many students close to him, including famous colleagues eased this hardship. Today, he continues writing his famous journals, which meticulously record his life and copies of which are being stored in archives and with friends in several corners of the world.

We recorded two long sessions of conversation in Budapest in July 1999. Dr. Gajdusek appeared indefatigable during these meetings. The transcripts below contain somewhat edited excerpts from our conversations. I first asked him about his childhood, about his family background, and about his getting interested in science.

I had a strange boyhood due to an aunt who was from my Hungarian maternal side of the family, Tante Irene Dobroczki. She was one of the first women in *American Men of Science*; she was an entomologist in plant diseases. She made herself very famous in the early 1920s after her Ph.D. at Cornell. She worked at the Boyce Thompson Institute of Plant Research and was a pioneer in insect tissue cultures. When I was about 5 years old, she hauled me to her institute and down to Princeton University, to The Rockefeller Institute for Plant Research there and other academic laboratories. My aunt was a Bohemian intellectual of the 1920s and early 1930s. She was a close friend of many artists, poets, and writers and play actors in post-World War I New York City. She introduced me as a small boy to many prominent scientists in virology, plant pathology, genetics, and entomology. Dr. Kunkle and Barbara McClintock were among them. She married into the 17th century Dutch-American van de Water family in her 30s.

In my early teens, I met Schoenheimer and Rittenberg who were doing isotope-labeling studies of metabolism. We played chess and I used to beat them and that is why I felt self-confident and got arrogant. That was before they wrote *The Dynamic State of the Body Proteins.*

When I was 10 or 11, I was thinking of going into medicine and Dr. William J. Youden advised me to study far in physics and math. He was Professor of Math at Columbia and wrote a mathematics text for physical

chemists. I could also beat him in chess but I don't play chess anymore. When I was 6 or 7, Dr. Youden showed me how to break white light in Newton's pyramidal prisms and to perform time-color-change reactions with colloidal gold. He was a friend of Ronald Fischer, the statistician in England with whom I later clashed in New Guinea.

Once I asked Dr. Youden in the greenhouse, what would happen if instead of sunlight we would grow plants in light of different colors? Since then he let me run my own experiments in the greenhouse.

I was very small when I started reading about great scientists, biographies of Louis Pasteur by Valery-Radot and Marie Curie by her daughter, and of many other medical scientists in Paul de Kruif's book *Microbe Hunters.* I stenciled at the age of 12 his 12 heroes on the steps leading to my chemistry laboratory in our attic.

How did you then have patience for school?

My mother dragged me out of the school to learn various other things like Medieval art or Egyptian hieroglyphs or for a trip to Europe. She didn't have much respect for my grade school. By about 12–13, I was doing algebra, elementary calculus, and differential equations. I went to public school in Yonkers, in Westchester County, New York, then to Roosevelt High School between Bronxville and Yonkers.

Your parents?

My father was from Slovakia; he came over alone when he was a teenager, speaking no English, and worked as a bar assistant. He had been trained as a butcher's assistant in Vienna. Eventually he opened his own butcher's shop and then other butcher's shops, and helped found the Albany Packing Company. By the time I knew him he made more money in one year than I'll make in a lifetime, but he had had only elementary school in Hapsburg Slovakia. We could have fifty or a hundred guests for a weekend with Hungarian or Romanian gypsies playing music for dancing.

What was the religious background in your home?

I'd never heard of the Bible until I was about five. But my mother taught me all the Greek myths and I prayed to the Greek Pantheon. At about five she changed the rules and decided that we should go to accepted standard churches. So I went to the Synagogue, to the Buddhist temple,

to the Moslem mosque in New York, to the Presbyterian, Methodist or Lutheran Protestant or to Catholic or Seventh-Day Adventist or Unitarian churches. We picked the ones that had the best parties, the best soft drinks, and the best kids.

Which were they?

Usually the Catholics had the best parties and the Presbyterians and the Lutherans had the best music and dances, but the main issue is that it made me very strange. My father was Catholic, from Bratislava but he never went to church in America. My mother said, "Forget about the atheists; they have small minds because everybody who is a theist makes them just say, No. So, they are the slaves of the theists. Most intelligent people, artists, writers, doctors, scientists, are agnostic." Mother was smart. She was a social worker and she was good in linguistics and literature. She considered the agnostics a fraud who say they don't know but in reality they're straight Christians and Jews, and they are wishy-washy people who have no personal ideals and live a strict life of the culture and society that brought them up. If they were real agnostic, they would experiment with new social orders and moral codes. She also made us feel sorry for all the monotheists. She introduced us to the Koran and the Old and New Testaments late, after we knew Greek classics and Eastern mythology. Mother was Hungarian but she was a rebel from Hungarian and Western Hebraic-Christian culture.

So what are you?

I'm a pagan and proud of it. I have never embraced any faith or religion and always wondered how others could settle for a man-made God and superstition. I realized early that those around me needed this crutch for their relations with each other. I settled for polytheistic Pantheons of colorful Gods, such as that of the ancient Greeks. I spent some time in Slovakia as a child. To father's Slovaks and mother's Hungarians, I preferred to be among the gypsies. The rural gypsy boys in the 1930s didn't put on any clothes in the summer until they were about 10. We just ran around as we did in the farm in New York. On our grandfather's farm in Slovakia there were acres of poppies. You could shake them to see if they were dry, break them, and eat the ripe seeds. But the gypsy boys told us not to wait until they get ripe but to scratch the stem and lick or drink the milk. So I was an opium eater at six.

How did you start having ideas?

From my late teens I understood that bright people hang out with other bright people. This includes nonverbal bright people too. There are people who can never do it with language, who are even deaf. Bright minds shed bright ideas, like all bodies shed carbon dioxide and water, they fart and put out nitrogen, they put out urine, and they put out perspiration and feces. I subscribe to Linus Pauling's views that we shouldn't worry about the origin of our ideas because we can always go back one or more steps and trace our ideas to earlier sources. You don't go around and say, "Hey, you're just breathing my water vapor, my carbon dioxide." When I hear the expression, "Oh, it was my idea first," I've the image of a little man saving his shit in a bag. We used to make fun of the people who came around Caltech in the 1940s who talked about <u>their</u> ideas and <u>their</u> theories. We called them shit collectors.

I have strong opinions about ideas. I don't like people in any field of science or the arts who are wishy-washy and timid. I prefer people like Linus Pauling who have a hundred ideas, state them clearly, and are often proved to be wrong. They quickly abandon any hypothesis that is proved to be wrong, and spring onto new ones. Also, the human mind does not produce anything *de novo*. And any idea that doesn't allow itself to be changed is a worthless idea.

Pauling let his ideas be used by others, but some also say that he was not too meticulous in attributing.

No, no, Pauling never attributed at all. My association with Pauling and his family goes back to 1940. He asked me to join him at Caltech when I was an intern in pediatrics at the Babies Hospital of Columbia Presbyterian Medical Center. I worked nights, weekends in the lab of Dr. Michael Heidelberger. I had a small room in the hospital and once I went into my room and found a foolish little old man sitting on my bed; I was 22 and this was in 1946. He jumped up and introduced himself as Linus Pauling of *The Nature of the Chemical Bond*. I thought this man was a psychiatric patient who strayed from his ward.

Was he already famous?

In my crowd he was. I grew up on *The Nature of the Chemical Bond*. I had its first edition with his signature. He knew of my work with John

Edsall at Harvard and Michael Heidelberger in New York. What I didn't know was that Pauling had had acute glomerulonephritis and almost died. A physician, Dr. Addis treated him with calcium glutamate for his condition. Linus thought that Addis had saved his life. To anybody who says that Pauling got senile and crazy over Vitamin C, I say, no, he was weird about medicine all his life. When we met in 1944, he was talking nonsense about medicine along with brilliant chemistry. He picked collaborators who weren't up to what was really happening in medicine. When he asked me to join him in California, I told him that I would like to go out to Caltech in a few years time after I completed my pediatric residency, and had arranged to do my Ph.D. in physics with Millikan at Caltech. Pauling told me right to my face, "No, you're not." Just like that. He then told me quietly that Millikan was becoming senile. Then he repeated, "Come, and join me."

Did you?

When I finished my residency, I did go to Caltech to work with him. At Caltech I lived in the Athenaeum; Aage Bohr, Jack Dunitz, Benoit Mandelbrot, Gunther Stent, Jim Watson, Ellie Wollman, Wolf Weidel, and many others were in our group. We were greatly influenced by Linus Pauling, John Kirkwood, Max Delbrück, George Beadle, James Bonner, Zechmeister but by then I saw Pauling much less than I'd expected because he was busy with politics. I worked more with John Kirkwood.

How did you get into government service?

In 1950, few labs in the world had tissue culture. It was also the start of the Korean War. John Edsall asked me to go down to Walter Reed Army Medical Service Graduate School to see General Smadel who was a civilian Director of Microbiology at the Army Medical Science Graduate School (AMSGS). Smadel said that we might lose this war if we wouldn't set up tissue culture growing facilities for virus studies. He asked me to be in charge of the tissue culture lab and go to Japan promptly. I was not interested in the job and in the war; I was leaving for Paris in a few weeks. Smadel had never in his life met anybody who told him, "No." I left for France and a few days later I was drafted. When I arrived later for duty at Walter Reed, Smadel, instead of being mad, had a colonel to be my logistic person; I had only the rank of captain. When Smadel saw me dressed with a civilian tie on my military uniform, he told me

to get out of it and never to wear a uniform. In the haste they also forgot to administer my oath of allegiance.

In 1950, we had the problem of hemorrhaging fever with renal syndrome in troops in the Korean war. I found that this was the same disease that killed many Japanese and Russians in the 1905 Russian–Japanese war. It was also a big problem in the Russian conquest of Siberia. There were fifteen hundred cases of albuminuria from a nephropathic epidemic in the German troops in Northern Finland in World War II. I guessed that there must be a low virulence form of Korean EHF in these troops in Finland. I set up the tissue culture lab to try to isolate the cause of epidemic hemorrhage fever (EHF) in our troops in Korea. During this period I wrote a book about the Soviet and Japanese early encounters and study of EHF in Far Eastern Siberia and Manchuria and their study of other hemorrhagic fevers.

I would like to ask you about the disease-related significance of protein structures.

I was recently asked to give a lecture at the Department of Physics at Trinity College, Dublin, responding to Schrödinger's question, "What is Life?" I gave my lecture the title, "Replication: Nucleation, Conformal Change, Self Assembly." I simply wanted to explain what happened in biology in 50 years. I emphasized the fact that we can now talk in a general way about replication, organic and inorganic. You require nucleation even of bubbles in boiling water. Even the process of formation of galaxies, black holes, dark clouds, solar systems, star clusters, glaciers, mountain ranges, diamonds, rubies, emeralds, the twinning of quartz, requires nucleation as the first step. The general rule is the bigger the nucleant, the more of the nucleant, the faster the process. A corollary is that steric hindrance interferes with the process if the nucleant is much larger than the monomeric subunit. But there is not much else we can say about nucleation; the applied scientists have taken it over; there is no good general theory of nucleation and geometric matching because nucleation involves a myriad of possible forms. You can't enumerate how many possible diamonds there may be. No two are alike and never will be.

Biology is now becoming aware of this issue. Without nucleation a mammalian skeleton will not develop; bone can't be layed down without nucleation. Some time ago I quickly published several papers on nucleation in biology just for the fun of having the first papers using the word in

the titles. Then we found some earlier papers on nucleation in the literature, but the authors forgot to use the word in their titles and never got so indexed. My friends from Harvard and Caltech told me there is no silicon biology, but there may be almost as many tons of diatom skeletons as there are of petroleum. The Nobel Foundation published a book decades ago about the biochemistry of silicon. Silicon serves as a nucleant for bone.

Most serious thinkers about the origin of life gave up all nonsense of an ocean brew of purines, pyrimidines, and amino acids, activated by ultraviolet irradiation. The degrees of freedom possible in a true solution would never allow the existence of these large complex polymers without having them attached to a surface of a solid or of a semisolid membrane. Silicon and various calcium aluminum silicates make long strings of hydrogen bonds with biological macromolecules. So the crystal lattice of silicon oxide, calcium silicon aluminates, silicon magnesium oxalates, and so on, fit with polynucleotides, polysaccharides, polyfats, hydrocarbons, and polypeptides to so match as to form long series of hydrogen bonds. Now, this may be no accident. If you take compounds of other atoms, like boron or the ferric series, there's no way you get this precise matching. You occasionally get enormous accidents, like silver iodide and cadmium iodide matching water, and they use these salts to nucleate the clouds by epitactic nucleation. Macromolecules of biology when they were originated could not have had the degrees of freedom that they would have in a true solution such as in urine, spinal fluids, or blood plasma. Nowhere in any cell from the Protozoa to man do large molecules interact fitting perfectly the laws of reaction in true solutions. Even diffusion through a membrane of large molecules is modified because the tight intermembranous spaces provide limited degrees of freedom for their movement. All big molecules of nature in a true solution are in emulsion or on a surface. It's hydrogen bonds with van der Waals forces and coulombic forces that keep the whole thing together. They don't have the freedom of translation and rotation of the dilute solution. My thinking in chemistry, biochemistry and enzymology is based on this. These macromolecules move in crowds down narrow paths or between tight walls in nature.

Curt Vonnegut's *Cat's Cradle* made everybody aware of the importance of nucleation and led almost everyone realize that each ice crystal or snow flake needs to be nucleated. Biology is never dealing with perfect crystals. Biological solids are all defective; they're not perfect crystals, but partially amorphous. We're dealing with amorphous solids or semisolids. This is also why strong physicists rarely go into the field of biophysics. I joke

about this all the time with my medical people. If you want to get a Nobel Prize in physics you better be sure you never put over five variables in an equation, but if you have only five, or even fewer, it's of little use in biology.

Does anyone think that there's no replication in astronomical cosmology? The moment you find your next five radio or light galaxies, people are going to classify them, they're going to fit in to one of the known types of galaxies. There are just a few dozen of myriads of possible structures. It's just strange that millions of light years apart this new galaxy will have one of the structures we already recognize, as close as any two diamonds, and certainly not random.

Glaciers will never be mapped by Newtonian physics but by fractals they will be. In order to apply Newtonian physics you have to declare that you're not interested in the individual and you're only dealing with the sum of Avogadro numbers of events. But who cares about 10^{23} when I'm worried about my glacier, my avalanche, my earthquake. Benoit Mandelbrot and I have been friends since before he created the idea of fractals. At Caltech we all knew that Benoit is the smartest among us. Many conventional mathematicians are furious about Benoit and his fractals and they should be; all scientists resent fractals. If you work on predicting sites of damage to the central nervous system by clots or pulling off thrombotic red cells that block a vessel, you are not concerned with exactly where it happens. But you do care when it happens in your own language cortex. This is where the fractal modeling helps. The same is true for infarcts in the heart, and for traffic patterns around great cities. When you use fractals though, there's one taboo question. That's "Why?" But it's still science because science is prediction, accurate prediction. Fractals predict patterns as accurately as any science.

Fractals predict what happens when you smash a cup against the wall; Newtonian physics won't do as well. But, suppose that you have the computer power to predict such events by classical physics. The next cup is smashed and you have to start it all over again. With fractals you have the whole thing.

Even in botany where you, seemingly, get only pretty pictures, it's more than that. Eventually, you take these billions and trillions of bits and hundreds of hours of computer time and you stop the display when it starts looking like ferns and palm trees. You never enter in any cell theory, any DNA, any Krebs cycle, any biochemistry. You enter minute changes in probability and density and distances between displayed points.

What is their relation to science? Your own healthy curiosity stops at what you like. When you change your functions, you get abstract art from the previous ferns and palm trees. Then you change your probability functions less and you have beautiful apple trees and peach trees. You may mimic conditions just as they are changing when you go up to alpine climates. The botanist sees you're modeling exactly what's happening. You can also look for funny things and you find them. The trouble is there is no Newton in there, no Bernoulli, no Schwan, no Darwin.

There has been some confusion in the terminology of even some of the most fundamental concepts, such as what is a virus and the gene?

I use the word virus also for what some others call prion, and I also use it for industrial viruses, and for computer viruses. There were professorships of virology in Vienna and Berlin before there was any DNA in the world and viruses were defined before there was an electron microscope or any knowledge of their chemical structure.

Virus and gene are strong abstract concepts independent of their chemical nature. The gene is the unit of evolutionary selection. The gene was with us from early in the last century with corn geneticist, Barbara McClintock types and Curt Stern types working on *Drosophila*. Incidentally, a German neuropathologist, Oskar Vogt, was asked to study Lenin's brain; he became Rector of the University of Petrograd before it was changed to Leningrad. He came back to become Director of the KWI Laboratory of Neurohistology. He never left Germany in the Nazi times but he refused to kick out the Jews from his Laboratory, so Hitler kicked him out, but he wouldn't leave Germany. He got a million dollars from the Rockefeller Foundation and bought himself the highest mountaintop in the Schwarzwald. There, in Neustadt, he founded his Institute of Brain Research, half French, half German. This was because his wife and co-worker Cecile, from Alsace Lorraine, refused thereafter to speak German. They published an important journal in the field. That was a unique private institute. Even when I came out with the kuru brains, nowhere in the world could we get a microtome that could section the whole brain in 18,000 sections. We had reason to look for β-pleated amyloid plaques in the few brains that didn't have such plaques. So the only place to do it was there. They were 93 years old; I had thought they were dead but they weren't and they had the microtome. Our only whole brain microtomes in the U.S. at the time were at Harvard with Paul Yakovlev and one tied up in California at

computerized brain cytoarchitectonics. The Harvard microtone made rough irregular sections, much too thick. I went to Neustadt in 1958 and worked with the Vogts. They died soon thereafter.

Getting back to the definition of the virus and the gene ...

The gene and the virus are high-order abstract concepts, independent of chemistry. The virus is any invisible submicroscopic particle that requires for its replication the energy system and the information system of the host. That defines viroids, prions, industrial inorganic viruses, computer viruses, infectious β-pleated (amyloid) nucleants, amyloid enhancing factors, and inorganic nucleating casts of these infectious nucleants.

Did you chart your career in any way in your youth?

I did when I was a kid. That was because of William Youden and Schoenheimer and Rittenberg, and my early reading. I was not even in puberty when William Youden and others convinced me that the future of medicine and medical research was going to be based on physics and math so I decided to go into physics and math and then medicine. I even wrote an essay about it when I was ten. I think of myself as a monster because I now feel sorry for kids who plan things far ahead but this is what I did. I planned.

What do you think of computer modeling of the living organism?

Absolute nonsense. It's a good way of beginning to think that way but you are never going to find anything in a neuron that works algorithmically. It's as bad as describing *Eine kleine Nachtmusik* in words, or to write a score for Liszt in Chinese ideograms.

You are not a reductionist.

Absolutely not. My attitude is, reductionism is an egotistical farce, it's mental masturbation. The idea that $E = mc^2$ explains everything is nonsense. It explains no human curiosity. It is too great a generalization to satisfy our curiosity about specific events.

So where does progress lie?

When I sit with the New Guinean savages, their jokes are as sophisticated as the mind play of Ionesco. I've taken a hundred kids out of Stone Age setting and some of them are now ambassadors for their countries,

they've gone into political science, politics, diplomacy, medicine, teaching, even higher mathematics in a third of a lifetime. They've no trouble with modern culture. There's zero change in human intelligence in a million years and it won't change in the next million. We must be cautious not to drive it down in individuals with our computers. Our verbal intelligence is the simplest kind of intelligence. Intelligence that it takes to run down a deer, to cut him off, to keep putting one's foot down and know when it's a snake, a stone, a tree root, a vine, a pit, and respond accordingly, is orders of magnitude more complicated than any monetary calculation we do in commerce or anything we do with languages. Just to sit here and not jump up because your *déja vue — jamais vue* programming detects no needle under your seat is using more brain than listening to me. We in science think that language is everything. That's as foolish as telling me to write down your kid's dance and asking me to translate music or dance into words. Nonsense. Spoken language and non-verbal messages are not commensurate.

Back in the 1950s, we visited the National Gallery of Art in Washington to study up close various schools of artists, especially Impressionists. From up close, within 10 centimeters, you often cannot even know what you're looking at. Then you get 3 meters away and you see that what purple, orange and black slabs, and green and gold globs of paint were in an Utrillo, is a rainy day with coaches coming down a street in Paris. Here was a fine example of coding for visual perception; score writing for vision.

What do you consider to be your most important contributions?

If I just list the fields in which I feel I made my major contributions, it is not for these for which I won the Nobel Prize. I think the most important field to which I've made my contribution is in variation in cognitive function of the brain — variability in brain programming for a given task in modern society and in stone-age peoples. That's the study, which encompasses even my crystallography and molecular genetics, slow virus diseases and Alzheimer's and Creutzfeldt-Jakob disease laboratories. The basic name of my section at NIH for 47 years was Study of Child Growth, Development and Behavior and Disease Patterns in Primitive Cultures.

The next most important thing I did was that I investigated the fact that the Claude Bernard experimental method is the worst of all approaches

to science when you're dealing with nonrecurring events. It is unreasonable to test any theory on a nonrecurring event. No matter what your results, somebody can say you cheated or it's a lie. So why do so? I published in *Nature*, back around 1959 or 1960, a thesis on the study of nonrecurring events. I felt embarrassed because the people that used that paper later were NASA and astronomers. You don't wait hundreds of years for an unusual comet to come back or a mysterious cosmological event to reappear. Everything happening when I walk into a Stone Age community that is thousands of historical years behind our civilization technologically is changed by my very approach when they see me. Everything that occurs is never to occur again. I was thinking about this in our work using sound and cinema recording and found the need for random scanning at human scale instead of directed hypothesis testing. Observations directed by hypothesis are the least valuable observations. Just observe, scan and gather data and try not to observe from only one theoretical point of view.

I think those are perhaps the most important contributions I made in science, all of them back 50 years ago.

Back in the 1940s, I worked with Michael Heidelberger at Columbia University College of Physicians and Surgeons on the autoimmune reactions. Then I left the field and I worked on tissue cultures; I first used tissue cultures for a whole bunch of viruses, including herpes simplex and Venezuelan equine encephalitis viruses. Then when I went to the Walter and Eliza Hall Institute with Frank Burnet in Melbourne, Australia I started to work on influenza virus genetics. I had wanted to work on infectious hepatitis virus but he didn't want me to work on it because it's a dangerous virus. Later he let me work with it and I found some peculiar autoimmune reactions in hepatitis patients. In developing the Autoimmune Complement Fixation (AICF) test I started immunology at the Walter and Eliza Hall Institute; previously it was all virology. I published in *Nature* a set of papers on autoimmune antibodies to various tissue components in hepatitis infections and yellow fever and in multiple myeloma patients. It was using that data that Burnet, on his return, changed the Institute to immunology, but he credited me for that. I would never have stated explicitly that each patient with multiple myeloma had a different clone of antibody producing cells. That was the indication of the clonal hypothesis of antibody production. Mac Burnet was smarter than I in using my data.

I had worked earlier on arboviruses in South America and I found a new subgroup of arboviruses killing people. Later I had for many years

Carleton Gajdusek: I am surrounded by kids, patting me. This image is from Tongariki Island in the Shephard Island Group in then New Hebrides [now Vanuatu]. Strangely, it is a site I worked on and camped in, which no longer exists on earth. It fell into the deepest of the Pacific in the violent earthquakes of the 1960s. Tongariki is where I discovered Hemoglobin-J Tongariki, which has an island migration on an arch of over 10,000 kilometers from above to far below the equator. It traces human migration of thousands of years ago! To have kept my notebooks and diaries on a site that now exists only in the Sky, I find as really wonderful (photography courtesy of Carleton Gajdusek).

the unique hantavirus laboratory in the U.S. in which we isolated worldwide most of the first dozen hantavirus strains and characterized them serologically. Ho Wang Lee, the discoverer of hantaviruses, sent me his student Pyong Wuo Lee and others from his hantavirus laboratory in Korea. He and Pyong Wuo Lee had first isolated the virus causing Korean hemorrhagenic fever. It was with the Koreans in my laboratory that we plotted out the world hantavirus distributions from China to Scandinavia and in the U.S., the Balkans, Australia, Oceania, and South America.

You seem to have been always on the move.

That's a snide legend. Yes, I am often introduced as the peripatetic pediatrician. Yet back in my laboratory I am often there for 18 hours a day or more. I use the time from midnight to morning to learn everything that's going on in the lab. I inoculated every chimpanzee and most monkeys,

with Joe Gibbs, with my own hands, all three thousands of them. I did much of the protein chemistry and virology. I've been at the bench for years. I rarely wrote a grant proposal in my life; I never wrote a funding request in my life; I never went to administrative meetings. All lab chiefs at NIH went to dozens of lab chiefs meetings a year; I attended but a few in 45 years. I never once submitted a budget; I never knew within a million dollars what my budget was; I never read my budget. I ended up with tens of thousands of dollars unspent and I never cared. So I was illegal about everything. I never knew within ten thousand dollars what my salary was. I lived half my life during 45 years abroad but so did many of my staff because most of our problems were in remote areas. I went on most of my trips without asking permission. But I had wonderful coworkers who could tolerate the administrative aspects of modern science better than I could, particularly Joseph Gibbs. I've always had support; good people supported me, Joe Smadel, Frank Burnet, John Eccles, Max Delbrück, Linus Pauling, John Kirkwood, Michael Heidelberger, Robert Loeb, Ashley Weeks, Rustin McIntosh, John Edsall, John Enders, Albert Sabin, Kattie Dodd, and Joe Warkany.

Were your trips, your work abroad primarily to help those people in remote areas?

Zero. That's all nonsense. That wasn't our idea. It was to limit variables in studying problems of man. You go to any small group, a village of Sami People in Finland, to a group of Indians in Mexico, a group of American Indians camping out under a bridge in Oregon, a group of gypsies in Kosice, Slovakia, and you will find that their diet differs less from each other than the diet of different children in any urban school in Europe. Even when we work in New York City or Budapest, I would only work with the gays, the lesbians, the gypsies, the Hmong or Kosovo immigrants, circus people, the street people, Hassidic Jews, the Jehovah's Witnesses because they are urban isolates and live together and they all have a more uniform life style than the more cosmopolitan urbanites. They form isolates within the metropolis. Controlling variables, that's the reason why I go to these isolates, that is the reason why I went to the remote and primitive populations. And to search for variance in human culture.

Did it cause you any problem to cross national borders so frequently and often between unfriendly nations?

Less than one might imagine. I never let myself be debriefed by the CIA or other security groups. I keep no secret. That way my style of operation has worked. I took most doors out in my laboratory. There were no doors. There were no locked files. I know that what happens once you have a closed door is that people go to sleep, or don't come to work, or they sneak in an interesting visitor who should see everybody and sneak him out without allowing others to share the visitor.

At home also, I would never have a secret from one of my kids in my life. When the kids began locking their doors, I took all the doors off, even to the bathrooms.

What kind of science do you respect the most?

I don't respect that part of modern science, which has been made into a soccer game. I have too high an ego to go into a game. If what you're doing will be done by somebody else in the next ten years if you don't do it, stop doing it. I don't call that creative science. I do a lot of that too, it's the bread and butter for Ph.D. candidates and young postdocs who must publish; we just have to do it but I don't respect it. Riddle solving is not the intelligence I most admire. I don't think much of the intelligences of the grand masters of chess. It's competitive masturbation of intellect. I gave up chess; I don't like the whole idea.

I find fun in science only when I am thought to be a charlatan. You don't know what you are doing, you don't know what questions to ask, you moll it over and you have foolish ideas for ten or twenty years, you talk to your colleagues and they don't get it and get bored. That is the creative process of science. When you know what questions to ask and how to approach them and can finally get your colleagues excited and they run home to write a grant proposal, you know you've done your job and you move elsewhere.

The biggest damage to diabetics research was Banting and Best's discovery of insulin. It caused 50 years of little work on the cause or prevention of diabetes; only studies on physiology of insulin, production of different insulin pharmaceuticals, desensitizing people who are sensitive to insulin. This has nothing to do with ever preventing or curing diabetes. The same with multiple sclerosis. Today we know no more about the cause than we did in the early 20th century. The same is for schizophrenia. I am waiting for the 18-year old to come into my office, saying, "I'm going to give my life to find the cause of schizophrenia."

How do you feel about the availability of genetics information and about gene therapy?

Just take manic-depressive psychosis. That's a very common disorder. It is in families most of the time. Charles Dickens had it and so did Ernest Hemingway, Berlioz, and Chopin. One third of the great musicians in the world have had this disease and almost one third of the great writers in German and English. My close friend Kay Redfield Jameson, Professor of Neurogenetics at Johns Hopkins and a world authority of the disease says in effect, Yes, I would want gene therapy. If in my amniocentesis I would be carrying the gene, I would keep the baby. I would be more interested in bringing up interesting people who would take lithium than borderline people of the norm. That's value judgement, just like religion. She threw a huge bombshell into the whole of genetic counseling.

About a couple of decades ago there was a meeting in Japan on the ethics of genetic counseling. Being a pediatrician, I was rocked by what at the end of the meeting the MD/Ph.D. students told us. It was something like this, We, as Japanese medical students think that no parent should have the right to know the genomic structure of his child. In our culture, if we had any of the diseases Dr. Gajdusek talked about, every one of our parents would change their will and we wouldn't be here in medical school. So don't tell us that it has anything to do with the good of the patient. The patient doesn't want to know. People want to know but not for his sake but for the family's sake. It's for the insurance company's sake; for the government's sake, or the military's sake. That isn't medicine. You don't go to the doctor to help your family or to help humanity, or the insurance company, the government, or the military.

Who are your heroes?

The first hero I've always had has been Socrates and then his alter ego, Alcibiades; then, always, Leonardo da Vinci and Michelangelo. I thought of Vergil but I gave him up. I always had Dostoyevsky and carried his picture in my wallet pocket from 13 to 73, but later I decided that he was too Christian, that I had made a mistake. Chekhov is now more to my liking than Dostoyevsky. I never liked Tolstoy. As I get older, I'm recasting my judgement. I could never accept Hebraic-Christianity. My attitude is that the Egyptians did beautifully until one crazy Pharaoh Akhenaten (Amenhotep) decided there was one god, himself, the Sun god,

and tried to destroy all the earlier monuments and records of Egypt. That's perhaps where the Hebrews later got their one God.

Sometimes I wish I didn't have my own parents and that Montaigne was my father. Goethe, I used to like, because he was such a pagan but then I found him pompous and his science bad. Now that I'm rereading him in the last 20 years, I find that he was more than I thought he was. In science the most important American who ever lived was J. Willard Gibbs who produced thermodynamics. All the rest of thermodynamics, ever since Gibbs, was just icing. Among Americans I would settle for Emily Dickinson, Edgar Allen Poe, Walt Whitman, and Herman Melville. As scientists, Linus Pauling.

Your heroes in a more personal sense?

Dr. William Youden and my aunt, Irene Dobroczki.

Would you care to add anything to the prion controversy?

I always joked with Charles Weissmann in Zurich that he had published papers defending his views, which were too complicated to be real. In each paper he made them simpler. Finally, he got down to the Prusiner, the Weissmann, and the Gajdusek hypotheses. Now he says that it seems as if Gajdusek's simple nucleation-crystallization idea is right. This is not pleasing because the Gajdusek, the Prusiner and the Weissmann hypotheses are tautological ideas. It is all the same nucleated β-pleated conformational change, as in any nucleation of conformational change to amyloid and fibril polymerization or crystallization. The hypotheses are all tautological. It's the geometric matching of nucleation and millions of different things can do it, even ground glass, frozen CO_2, even a spark and also an inorganic molecular cast or atomic ghost replica. So when Weissmann says that I win, I feel disappointed to have people credit me with a theory that is not different from others'.

According to some, Charles Weissmann should've shared the prion Nobel Prize.

That was unfortunate; yes, he should have shared with others: Tygve Alper in London and Raymond Latarjet of the Curie Institute in Paris who proved that there was no DNA or RNA in the scrapie agent. They did the work on scrapie ten years before I entered it. I joined Latarjet to prove the

Pope John Paul II and Carleton Gajdusek (courtesy of Carleton Gajdusek).

Fiedel Castro and Carleton Gajdusek (courtesy of Carleton Gajdusek).

Kuru patient and Carleton Gajdusek (courtesy of Carleton Gajdusek).

same for kuru and Creutzfeldt. Raymond Latarjet and Tygve Alper published in *Nature* and *Science* forty years ago that the scrapie virus has no nucleic acid. Ian Grasser and Pavel Albrecht showed immunologically that the infectious material of very high infectivity later was non-antigenic. Thus we have known since the 1960s that the agent contained no non-host antigens, i.e., no antigenic macromolecules.

Have you ever nominated them?

I didn't. I was just too busy with my own career. Now I'm doing things like that.

Some people say it's better not to study the literature, rather, get right to the frontier and make your discovery.

I have said that myself, too. The course is too long. I've learned that I can take my teenagers who had been suspended from school; it takes me one week to teach a teenager how to sequence nucleic acids and how to operate the computer and our synthesizers. That isn't the intellect of science, it's just manipulating machines.

Can you make a discovery this way?

Everybody is doing it; we did too. When we got the new viruses I was using weekend nonscientific New Guinean kids doing various operations and they were more accurate than many of us.

Did you put their names on the paper?

I do not think that authorship should include anyone who cannot discuss and defend all aspects of a paper. We named virus strains after them. The girls who wove carpets and made pre-Colombian laces were illiterate and yet create far more complicated patterns than we do. If you examine the laces from over 2000 years ago from the wrappings of Peruvian mummies, they have intricate woven figures that are as complicated as anything in modern topology.

What's the lesson?

That there's been no progress in the human brain and in human creativity and in the ability to think in the last hundred thousand years. It would take a few weeks for an ancient Chinese philosopher or Kant to catch up with nuclear physics and modern biology in terms of concept. I've proved this in my family with my preadolescents springing from Stone Age to modern high tech culture. That's my biggest contribution, that youth can jump 20 to 30 thousand years from cultures that had no metal, no grain, no agriculture, can produce Ph.D. mathematicians and physicians and surgeons and inspired modern artists, actors, poets, jurists, and statesmen.

Do you suggest following your example of taking children out of Papua New Guinea and Micronesia?

They'll do it themselves. If they don't, their language and culture will now quickly become extinct. But only a racist colonialist would educate them to become doctors and teachers. What they really need is lawyers, engineers, and bankers. And most of all they need pride. Pride comes from seeing that members of their group may become famous athletes, writers, artists, statesmen, actors, businessmen, scientists, and teachers by world standards and this can be accomplished abroad more easily than from returning home to improve the conditions of life there. They must do what Hungarian Jews and Chinese do on this score.

Carleton Gajdusek during the interview (photograph by I. Hargittai).

What else do you suggest?

There's a vast amount of philosophy that's treated seriously and that should be abandoned. It is much like the general concept that deaf people are a little inferior. But a congenitally fully deaf person can be as bright as anybody if he's not converted to speech and thereby ruined, by trying to make him learn spoken languages that he is not equiped to use. It has to do with his nonverbal cortex and learning without a coding system that is commensurate with spoken language.

Is it a waste of time to teach deaf people to speak?

It's more than that; for the congenitally fully deaf it's criminal.

What will be your legacy?

The most important legacy is this. Plato and Aristotle, Rousseau and Nietzsche, right up to Wittgenstein and Gödel have made the condescending nonsense that so-called primitive peoples have a different kind of brains,

and have basically different thought process and abilities than modern civilized man. My Mikes and Moros have proved that preadolescents from a Stone Age New Guinean Culture can enter the modern high tech age as engineers, physicians, surgeons, high school or university teachers, jet pilots, artists, or computer freaks, earning our own university degrees with only two decades exposure to civilization. Not only that some can, most can. I'm obviously more proud of this than of any of my science. My being able to find that people from Stone Age cultures can make the leap of more than 20,000 years of cultural history in a lifetime, from a culture level earlier than the ancient Greeks and Egyptians and the Altemira and Lascaux cave painters to modern arts and science.

The problem solving demands on the human brain were surely as high in the Arctic when people had to figure out how to kill a mastodon or whale near to their dwelling, or when cave artists had to reach the ceiling of their dark cave to paint, or when man figured out how to survive in a primeval jungle as with us in modern high tech societies. When he set his patterns of kinship, rules to regulate his aggressiveness, discovered his language, and formulated his behavior to respond to his sense of joy and fear, his passions and his sense of awe and wonder he did so as wisely and with as much intelligence as we try to do today. We have really no advance in our cognitive abilities in these past 20,000 years. I've always played in science. I've never worked. I don't treat science any more seriously than other aspects of life. I think it's a game of fun.

Charles Weissmann, 2000 (photograph by I. Hargittai).

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Charles Weissmann

Charles Weissmann (b. 1931) is Senior Research Scientist at the Medical Research Council (MRC) Neurogenetics Unit, St. Mary's Hospital in London and Professor Emeritus of the University of Zürich. He received his schooling in Zürich, earning his MD in 1956 and Ph.D. in Organic Chemistry in 1961 from the University of Zürich. Following a stint at the Department of Biochemistry of New York University (1961–1967), he spent the major part of his professional career at the University of Zürich where he was director of the Institute of Molecular Biology.

He is a Foreign Member of the Royal Society (London, 1983), a Foreign Associate of the U.S. National Academy of Sciences (1989), and a Member of Academia Europaea, received the Ruzicka Prize (Switzerland, 1966), Otto Warburg Prize (Austria, 1980), Heineken Prize (Amsterdam, 1982), Scheele Medal (Uppsala, 1982), Gabor Medal of the Royal Society (1993), Robert Koch Medal (Germany, 1995), Max Delbrück Medal (Berlin, 1997), Mendel Medal (London, 1998), and numerous other distinctions. He has served as officer or member of many boards and committees, just to mention a few, he was Chairman of the Scientific Board of the Biogen Company (1984–86), Associate Editor of *Cell* (1983–88), Chairman of the European Commission Group on Bovine Spongiform Encephalopathy (1996), has been President of the Ernst Hadorn Stiftung (since 1986), and Associate Editor of *Molecular Medicine* (since 1994).

Charles Weissmann and his co-workers did important work in RNA phage replication and on gene expression in eukaryotic cells. His early achievements included the discovery of quasispecies, the development of site-directed mutations in biologically active nucleic acids, reverse genetics,

the first construction of infectivity-generating plasmids and insights into the replication of retroviruses. During the 1980s and 1990s, he was best known for his pioneering work on the first synthesis of biologically active interferon and on cloning the protein essential for scrapie pathogenesis and its role in scrapie infectivity. We recorded two sessions of conversation in February and March 2000 in London and started with Dr. Weissmann's latest interest.

Two years ago when we first met as lecturers to the "Frontiers of Biomedical Research" meeting in Indian Falls, California, another lecturer told me, "Charles Weissmann should have shared the Nobel Prize for prion." Would you care to comment on this?

It depends on the view you take on how one deserves a Nobel Prize. Stanley Prusiner got the Prize because he promoted this very unconventional theory that a protein could be an infectious agent. I say promoted because the idea was first proposed in 1965 by a mathematician, John Griffith, but I guess nobody took it seriously until Stan took up the idea and provided supporting evidence. It was well known by 1960 that you could transmit scrapie from sheep, where it was endemic, to goats, sheep and with some initial difficulty to hamsters and mice. Then some data emerged which argued that the infectious agent was devoid of nucleic acids, for example, irradiation with ultraviolet light did not inactivate the agent the way it does viruses or bacteria. Also, the action spectrum did not show the maximal inactivation at 260 nanometers that is typical for nucleic-acid-containing agents. So some people started speculating that the agent could be devoid of nucleic acid and consist of some other macromolecule such as carbohydrate, protein, lipid, and so on. Still, most scientists continued to believe that the scrapie agent was an unusual kind of virus which contained nucleic acid and that for some unclear reason this nucleic acid was resistant to radiation and difficult to isolate. In fact, to this day a number of scientists, mainly of the older generation, adhere to this belief. In view of the central dogma, which states that proteins are encoded by nucleic acid, it was difficult to imagine that a protein could replicate, which is what the infectious agent does. You put a small amount into an animal and after a while you end up with a lot. So how could a protein replicate?

John Griffith proposed that there is a naturally occurring host protein that can exist in two states, a normal and an abnormal one. In the healthy organism this protein only occurs in the normal state. If the abnormal

form is introduced into the organism, it can somehow cause the conversion of the normal into the abnormal form, resulting in a cascade of conversion. In fact, he proposed three possible explanations, of which this was one, but nobody believed any of it. Then, in 1982, Stan Prusiner, who had been working in the field for years, trying to purify the agent from infected brain by biochemical procedures, obtained a fairly purified preparation of the infectious agent in which he found a protein he called PrP scrapie, or PrP^{Sc}. He failed to find this protein in normal brain, so he was convinced that it was the infectious agent and that it could replicate. I don't think Stan was very aware of Griffith's paper or at least he did not think along Griffith's lines. I heard him give a talk in 1982 in Australia, at the International Biochemistry Meeting in Perth, in which he reported the isolation of PrP^{Sc} (at that time it was simply called PrP, because he did not yet know that there were two forms of the protein) and where he suggested there might be an as yet unknown mechanism which would allow a protein to be copied. I approached him after the talk and told him I couldn't believe that a protein could be made without being encoded by a nucleic acid, a messenger RNA. I was convinced that if one would look, one would find a messenger RNA that codes for this protein. Stan was very open-minded about it and we agreed to start a collaboration. This later included Lee Hood, a molecular biologist who partially sequenced the PrP^{Sc} which Stan had isolated.

We searched for the messenger RNA in Zürich and we found it, that is, we isolated the cDNA corresponding to it. That was done by Bruno Oesch. A diploma student, Konrad Basler, later isolated the chromosomal gene. Amazingly, although the PrP cDNA stemmed from the brain of animals suffering from scrapie, when we looked in normal animals, the messenger RNA was also present and at the same level. This posed a dilemma, because Stan had found the protein only in brains of infected animals. How was it possible that this protein was not found in normal animals? What I have not told you yet is, that when Stan purified the infectious agent from scrapie-infected brain, one of the first steps he used was digestion of the brain homogenates with protease. This was because he had found that infectivity was preserved under the digestion conditions he used, while a lot of protein was degraded. When we found PrP messenger RNA in normal brain, Stan and his colleagues did some more experiments and, using antibodies to PrP, found that both uninfected and infected brains contained PrP. However, when they treated uninfected brain homogenates with protease, the PrP was completely digested and disappeared, but in the infected brains

it was resistant to protease digestion. This showed that PrP in infected brain was different from that in normal brain. It was only then that we published the results of our collaboration in *Cell.*

What made the protein resistant?

To answer that question took many years of work. This was mainly work at Stan's lab; it showed that there was no chemical difference between the proteins, it was a conformational difference.

By chemical, you mean sequence.

Correct.

Please, define, what do you mean here by conformation? I have talked about the structural chemistry aspects of scrapie and BSE with others and there is a semantics problem. When people talk about conformational changes, this may mean different things to different people. In chemistry it relates to internal rotation, whereas in molecular biology it is used in a broader meaning. When conformational change in proteins is referred to, what is meant by this?

This term is used by protein chemists to indicate changes in three-dimensional structure. Many proteins have predominantly alpha-helical structure and most proteins can somehow be converted into forms rich in β-sheet structure; that is an example of conformational change.

Many years later, at the ETH Zürich, Kurt Wüthrich determined the structure of the normal form of PrP, which was meanwhile named PrP^{C}, by NMR analysis. It consists of three α-helices, a very short β-sheet structure and half the molecule is in random-coil form, which is unusual for proteins. I should add that this analysis was done with recombinant PrP obtained from *E. coli*, which, in contrast to PrP^{C} from brain, is not glycosylated. The abnormal form, PrP^{Sc}, could so far neither be crystallized nor solubilized without its losing infectivity; it's an aggregated mess. It was characterized by Fourier transform infrared spectroscopy and circular-dichroism spectroscopy and the conclusion was that the abnormal form has a lot of β-sheet structure, about 50 percent. The two forms have very different three-dimensional structure.

Most people continued to believe that the infectious agent was some virus, despite the fact that years of search had failed to reveal a virus or even a scrapie-specific nucleic acid and despite the demonstration of

biochemical linkage between infectivity and PrP^{Sc}. The discovery that PrP scrapie and PrP^{C} were both encoded by the same host gene did little to convince the scientific community of the protein-only hypothesis, although it was in line with one of Griffith's proposals.

The first genetic argument in favor of the important role of PrP in spongiform encephalopathies came from an important experiment carried out in Stan's laboratory and regarded the so-called species barrier. If you try to transmit scrapie agent from a hamster to a mouse, you find this to be a very inefficient process and it takes very long time until animals get sick, if at all. In most cases the animal dies of old age. But if one of these animals does get sick, and then you pass the agent from this mouse to another mouse, then it very rapidly comes down with the disease. Stan speculated that the conversion of mouse PrP^{C} by hamster PrP^{Sc} was difficult because the amino acid sequence of hamster and mouse PrP are quite different; there are differences in 12 amino acid positions. Stan had in the meantime built up a molecular genetics group; when I first met him he was doing only biochemistry. He had this very elegant idea that if you were to introduce the hamster gene into the mouse genome, that mouse should be much more susceptible to the hamster agent. In order to introduce the hamster gene into the mouse, you inject the cloned hamster PrP gene into a one-cell mouse embryo; with some luck, it will integrate into the genome and the mouse and its offspring will carry one or more hamster PrP genes. Indeed, the transgenic mice proved to be very susceptible to hamster prions.

The second genetic argument concerned the familial human transmissible spongiform encephalopathies. Most human TSE's, or prion diseases as they are now called, such as Creutzfeldt-Jakob disease, are sporadic, that is, they occur at random in the population and very rarely. However, there are rare families in which 50 percent of the offspring succumb to the disease, a clear indication that in these cases it is caused by a dominant gene. So the question was, what was the gene? Because Stan was convinced that PrP was part or all of the infectious agent, he took a guess that the gene that is mutated in these patients is the PrP gene. One of his collaborators, Karen Hsiao, examined the PrP genes in two families that had a familial form of this disease. Indeed, she discovered that there was mutation in that gene, that all the offspring that carried the mutation came down with the disease and the offspring that did not inherit that gene remained healthy. The gene is dominant; in other words, one copy of the mutated gene is enough

to cause the disease. That was a tremendous breakthrough, because it showed a direct link between the PrP and disease. That is to Stan's credit.

So that finding was, again, very important, but it still failed to convince the virus coterie. A lot of the other scientists who were not emotionally involved in the virus hypothesis were easier to convince.

Was not this a little the reverse situation to the one when Oswald Avery's findings about the transforming principle had a difficult time getting accepted because the conventional wisdom held proteins responsible for heredity?

You are exactly right. Then, most everybody believed that protein was the genetic material and DNA was supposed to be some junk — a storage form of nucleotides was one proposal. Avery showed the genetic material was DNA. In the early 1980s, everybody believed the scrapie agent was some unusual virus and we were claiming it was a protein.

At that point many scientists who were not directly involved in this research, who were not emotionally compromised, were becoming convinced. Many researchers, however, who had spent most of their scientific lives looking for a virus, found it difficult to accept that they had been looking for something that doesn't exist. There are a few of the old guard who are still reluctant to accept the protein-only hypothesis.

In the late 1980s, it occurred to me that if we could eliminate the PrP from the mouse, this mouse should become resistant to the disease and incapable of replicating the agent. When I learnt from Peter Gruss that he and others were beginning to develop methods to destroy in specific, targeted fashion individual genes in a mouse, I decided we should follow in their footsteps. One of my very talented collaborators, Michel Aguet, undertook to develop this method to knock out the PrP gene. Mario Capecchi and Oliver Smithies in the United States were successful in carrying out targeted "gene knockouts" and we learned essentially how to do these things from their work. Michel Aguet and a graduate student, Hans-Ruedi Büeler, carried out our experiment. It was a tedious, long, and difficult procedure at the time. Finally, we generated these mice and we were astonished by what we hardly had dared to hope for, namely, that animals devoid of PrP developed normally and were healthy. There were no obvious defects to these animals. This was very surprising because here was a gene that was conserved during evolution in all vertebrates, was expressed mainly in the brain and in many other organs, already early in embryonic development, and yet it could be

eliminated without causing damage. Why this is so is a chapter for itself. We were, of course, very happy because now we could do our experiments. The reason somebody said to you that maybe I should have shared the Nobel Prize, may have been because that was probably the most convincing experiment in favor of the protein-only hypothesis. One must be very clear though that what this experiment proves, is that PrP is essential for generating the infectious agent; it doesn't prove that it is the infectious agent, although this is by far the simplest interpretation.

I'm a rather careful person; I worry about making mistakes and we were very careful to point out what the experiment really meant. However, most people said that this proved that the protein is the infectious agent. It was certainly a good argument.

To summarize, we cloned the gene and we did this knockout experiment. Stan's merit was that he isolated this protein, which led us to PrP and to the gene; he showed the linkage between familial forms of the disease and the gene, and he showed the gene could facilitate crossing the species barrier. The additional merit of Stan is that he was very passionate about this. He was convinced that he was right even when nobody would listen to him, and he was subjected to a lot of hostility and vituperation. Some of the early work and early papers were not very convincing. Many of his experiments were not very clean and he tended to over-interpret them. This drew quite a lot of criticism. But the thrust of everything was correct. If you are looking at the relative merits, Stan was the person who carried the ball when nobody was willing to listen to him. I came in skeptical, but through our own experiences I became convinced that the protein-only hypothesis is correct. Our experiment with the gene knockout was the kind of experiment one does to falsify a hypothesis, and when this experiment spectacularly failed to do so, I was also convinced.

Stan was very intent on getting the Nobel Prize and he really worked hard at it. He asked people to propose him, including myself, which I did. As for myself, I felt that if there was merit in what I've done, it would be recognized without my having to do anything about it. And I did receive a number of other awards.

What is the relationship between the prion work and Gajdusek's work on kuru?

Gajdusek is a brilliant person, a polymath. He was sent to Papua-New Guinea to investigate kuru. At that time people didn't know whether kuru

was a result of poisoning by some plant or animal these natives were eating or whether it was a nutritional deficiency or whether it was genetic disease. Almost nobody thought it was transmissible. Gajdusek's big merit is that he showed that it is transmissible. He had done several transmission experiments and when nothing happened after a few weeks, the experiments were discarded. Usually, when something is transmissible, you see the disease after a few weeks, whether it's a virus or bacteria. Gajdusek collected a number of brain specimens and he sent them back to the States; they made the sections and they found the spongiform degeneration and the deposition of an amyloid in the form of what is called kuru plaques. Stan later showed that they consisted mainly of PrP^{Sc}. Those pictures then were exhibited in London and a man called Hadlow, who was a scrapie researcher, saw them and noticed that they looked exactly like scrapie. He published a short note in the *Lancet*, pointing out the similarity between scrapie and kuru and he also wrote a letter to Gajdusek. At that time it was already known that the incubation time of scrapie was extremely long, years or decades. The suggestion was that if kuru was like scrapie, it wouldn't be enough to wait a few weeks, you would have to wait a few years. Gajdusek and his colleagues followed up on this and after two years the inoculated chimpanzees got sick. Stan always points out that Hadlow should have shared the Nobel Prize with Gajdusek, because if Hadlow had not made his remark, Gajdusek would likely not have done the long-term experiment.

Would you like to add anything to the prion story?

The evidence is there and it is very strong. There is one experiment everybody in the field still feels should be accomplished. That is, to take normal PrP^{C}, either made biosynthetically or extracted from a normal brain and convert it *in vitro*, under controlled conditions, into an infectious form. This hasn't been done yet. Many labs are trying to do it, though.

A couple of years ago it was discovered that in yeast and other fungi, there is a phenomenon similar to prion disease. There are phenotypes that are transmitted not by genes but by proteins. In yeast there are several proteins that can exist in two conformations. In one conformation the yeast shows one type of behavior, one type of biochemistry, and in the other form it shows another type of biochemistry. These forms can be converted into each other in a test tube. In a way the work with yeast

has complemented the work with animals very beautifully. The yeast people speak of "yeast prions," however these proteins have no similarity to PrP.

Are you continuing your activities in this field?

Yes. One of our major projects is converting the normal form of PrP into its infectious counterpart. We are also attempting to determine the normal function of PrP.

How do you feel about animal experiments?

They are a necessary evil. I dislike them intensely. Giving prions to mice causes suffering. I've occasionally wondered whether if I had to do these experiments myself, physically, I would be able to do them. I guess I would, because in the prion field you currently cannot do without them.

Transgenic experiments are different; most of the transgenic mice we make are healthy, though not all of them. Then there are experiments, albeit not in our laboratory, in which one partially cuts the spinal cord of rats or mice in order to try and achieve regeneration. The mice and rats are half paralyzed; it's very unattractive but how else can one hope to find a treatment for paraplegics one day?

If we can now move to interferon, I would like to ask you, how did you pick this problem and what were your original expectations?

In the mid-1970s, I knew very little about interferon. I was in Zürich, working with RNA phages, retroviruses, messenger RNA expression in the eukaryotic cells, cloning cDNAs and attempting to clone the beta globin gene. Then one day, at a Gordon Conference, I met a friend with whom I had worked alongside in New York, called Peter Lengyel. He was and still is Professor at Yale University and he had been working on interferon for several years. This was 1977; recombinant DNA had just been developed. Nobody had cloned a gene yet. He was telling me how difficult it was to obtain interferon in sufficient quantities for any work. Nobody had yet obtained pure interferon.

What was so special about this protein that made people expect so much from it?

First of all, it was so difficult to obtain, so there was a lot of fantasy about all the wonderful things one could do with interferon if only one

had enough of it. It's an immensely active protein; the dosage one uses medically is 10 micrograms per individual three times a week. In nanogram concentration it can deeply affect the metabolism of the cell. Its specific activity is more than one hundred million units per milligram, the unit being the smallest amount that would cause a biological effect in cell culture. So I said to Peter, what we ought to do is clone the gene and express it in *E. coli*; at that time this had not been achieved for any biologically active mammalian protein. The problem was how to clone the gene if you didn't know the structure of the protein; there was no sequence, no antibody, not even purified protein. Then I thought of a strategy that would allow one to clone a gene without knowing anything about its structure, only knowing what the biological activity of the product was. The idea sprang full-fledged during a walk we took during the Gordon Conference, the concept was already perfectly clear. We decided to go ahead. For me there were two things of interest. First of all it was a technical challenge and the possible solution was a cute idea I wanted to carry out. The other aspect was that the interferon gene is strictly controlled, in other words, interferon was never expressed in measurable amounts except when a cell was infected by virus. I was interested in promoters and in particular how promoters were controlled. It seemed to me that if one could isolate that gene with its promoter, it would be a very valuable tool to find out how induction of expression works.

We soon started our collaboration with Peter Lengyel; he would send us RNA from virus-infected mouse cells and we would extract the messenger RNA and go about our strategy. We were moving rather slowly, because we had to learn a lot of technology that did not exist yet. Then, about that time, in 1978, some venture capital people from the United States visited me in Zürich. They wanted to start a biotechnology company in Europe, modeled on Genentech, but with European scientists. They had collected a few names of European scientists, among them mine, and they asked me whether I wanted to join this company. At that time I refused, but after a second visit, a year later, I reconsidered. There were to be two Americans participating in the company, Wally Gilbert and Phil Sharp, both of whom I greatly admired and were later to become Nobel Laureates. Sharp had discovered splicing, Wally had invented a way of sequencing DNA. These were two brilliant scientists and it was very attractive to me to join a scientific board with them on it. As the newly formed company,

Biogen, had very little money to start with, we decided that the scientific board members would conduct research in their own university laboratories, funded by the company. Wally Gilbert was going to clone human insulin cDNA, which hadn't been done yet, and express it in *E. coli* (he never succeeded), Phil Sharp was going to do pig growth hormone, Ken Murray hepatitis B antigen for immunization, and I interferon. Biogen set up agreements with the universities; my university set me free for 30 percent of my time, which was very generous. Biogen was paying for all the research plus overheads and the university would get a royalty if we cloned interferon and it were to become commercially successful. The scientific board members got shares of the company for joining the company. They were worth virtually nothing at the time but would become valuable if the company became successful.

Biogen wanted me to clone human interferon alpha cDNA. I had thought it would be easier to work on mouse, but in the event it proved to be much more practical to use human mRNA because, as I eventually realized, humans are bigger than mice and produce more mRNA per individual. I found out that there was a person in Helsinki called Kari Cantell who was making natural interferon starting out with human white blood cells. He collected cells from 80,000 liters of blood per year, treated them with virus, collected the supernatant, and purified the interferon to some extent. From all this blood he ended up with one gram's equivalent of interferon, at about 1 percent purity. Clearly, the cells from which he extracted the interferon would have to contain the interferon alpha messenger RNA that could serve as our starting material. I started a collaboration with Kari Cantell. He used the supernatant of the white blood cells to make interferon and we purified the RNA from these cells and went about our strategy. I had a Japanese postdoc called Shigekazu Nagata who then executed the strategy. A good idea and a wonderful worker produced results; within a year he cloned the gene and by the end of 1979, he generated the first, small amounts of recombinant interferon alpha from *E. coli*. There must have been a dozen laboratories working on this problem like mad, including Genentech and Cetus, and some of the biggest pharmaceutical companies. We beat them all by a large margin, months, and we patented the procedure of producing interferon in *E. coli*. The bottom line of the story was the following. Hoffmann-LaRoche, or more precisely, the now defunct Roche Institute in Nutley, had been working on natural interferon, and Sidney Pestka and a terrific collaborator of his, Menachem Rubinstein, from Israel, were

successful in fractionating and purifying interferon, for which they got a substance patent. We got a patent for the production of interferon in *E. coli,* which we ceded to Biogen as contractually agreed upon. Biogen sold the rights to Schering-Plough. As Schering-Plough had the production patent and Hoffmann-LaRoche the substance patent, they cross-licensed each other and eventually dominated the market for recombinant interferon alpha for the next 15 or more years.

Has interferon proved as successful as you had hoped for it?

Much more so. I expected very little of the medical applications. There are books about this story; one of them is called *Commotion in the Blood.*

At first interferon alpha appeared to be a big failure. There had been a paper by a Swedish scientist claiming that he could cure or at least prevent the progression of osteosarcoma and that made an enormous splash in the late 1970s. There were people in the United States who were pushing interferon as a treatment for cancer and interferon made the cover of *TIME* and *LIFE* magazines. It was thought that if only one could make enough interferon it would solve the cancer problem. I didn't see any particular reason why it should work so well, but in the event I was wrong. In the early 1980s, everybody in the field was depressed because there was a lot of interferon around, albeit still expensive, and yet there was no effect on osteosarcoma, no effect on breast cancer, no effect on colon cancer; everything failed. Schering-Plough and Hoffmann-LaRoche were trying very hard to get interferon into the market but there was no medical indication for it. The FDA did not approve interferon because its effectiveness wasn't demonstrated for any disease. The companies were sponsoring all sorts of trials, including treatment of the common cold by inhalation but nothing worked.

Then a guy called Quesada in Texas used interferon for a very rare form of leukemia called hairy cell leukemia, for which there was no treatment, and it worked almost miraculously well. This caused an enormous excitement. Both Hoffmann-LaRoche and Schering-Plough supported large-scale clinical trials on hairy cell leukemia and although patients were almost never permanently cured, it was possible to keep the disease under control. It was used until a few years ago; now there are better treatments. Because interferon alpha was then approved by the FDA, physicians started using it for all sorts of diseases and it proved to be active in other cancers, not a cure, but of considerable benefit for many patients. Sales reached

50–70 million dollars annually, which was nice but far from what the large pharmaceutical companies really like. The real commercial breakthrough came when physicians went back to using it on viral diseases, first on hepatitis B and soon thereafter for hepatitis C, for which there was no treatment. There was a beneficial effect in about 40 percent of the patients, but when treatment was stopped only 15 percent of the patients showed lasting improvement. Hepatitis is a very serious disease, it often leads to liver failure and hepatic cancer, so every person healed is a person saved, and if you happen to be among the 15 percent you are grateful. Then the sales of interferon increased almost tenfold; all of a sudden Schering-Plough was selling 500 million dollars worth of interferon and now they are close to a billion dollars annually. So it is a tremendous commercial success. Moreover, with improved forms of interferon alpha treatment, the rate of lasting cures has risen to 40 percent.

A few days ago we heard the news about cloning piglets. What is your reaction?

It was not unexpected. It works for sheep, it works for cattle, it works for mice, why shouldn't it work for pigs? It is true though, that cloning pigs was technically far more difficult that cloning sheep and cattle.

How about humans?

The principle has been established so it should be possible for humans too.

Would you favor it?

There may be circumstances where there would be a good medical and humanitarian reason to do it. I don't see that generating cloned humans in itself is very desirable, but the technology opens the possibility of generating tissues and even organs for transplantation. I don't have an ethical problem with it.

The argument is if you clone an individual, will he and his clone have identity problems? They will not. They are not the same people. If you clone Einstein, you won't get Einstein. You will get the substrate for an Einstein but he will never be Einstein. I sometimes wonder whether it might not be useful to have a couple of individuals with Einstein's potential around in every generation. Or with Mozart's.

Would you comment on the debate on genetically modified food?

A lot of it is ridiculous. I'm convinced that we can make greatly improved plants; a very nice example is the introduction of genes for enzymes required for making Vitamin A in rice. It required the introduction of four different enzymes. Vitamin A is a vitamin whose absence causes blindness. There is no danger to the environment in this at all.

I have more sympathy for people who say that resistance to herbicides might spread to weeds. But I have no objection to changing a plant to have higher nutritive value.

The issue has been very badly handled. Monsanto launched these plants with herbicide resistance and insecticide resistance. Genetically modified Soya, for example, has become very popular with farmers because it improves the yields. The farmers benefit, Monsanto benefits, only the consumers do not benefit. If the price for these genetically modified products had been lower than for the natural products, the consumer would have benefited as well and it would have taken a lot of wind out of the sails of the opponents.

You chaired a European Commission Group on Bovine Spongiform Encephalopathy (BSE).

It was a chore and I tried to get it done as quickly as possible. We worked on a purely scientific, non-political basis, that is, disregarding national interests. The result was a fairly comprehensive report about the kind of research that should be done in the field. The European Commission then created an agency to fund projects that had been recommended by the commission.

Your C. V. mentions some work related to AIDS and Alzheimer's disease.

We worked on retroviruses but not on HIV. These retroviruses included so-called tumor viruses and I was specifically working on Rous sarcoma virus and avian myeloblastosis virus. Our work cast light on aspects of the mechanism of replication. Interestingly, some of our earlier work on phage Qbeta proved to be relevant to the problem of development of resistance of HIV to drugs.

We had been the first to find that a virus population is genetically very heterogeneous. We found that if you propagated a phage population for ten or twenty generations, only about 20 to 30 percent of the virus particles

had the so-called consensus or standard nucleotide sequence, while 70 percent had one or more nucleotide changes at any one site within the genome. You could find almost every possible single mutation in a liter of phage lysate. This needs some elaboration.

If one determines the nucleotide sequence of a viral nucleic acid, what you determine is the average sequence. For each position you determine the majority or "consensus" sequence but if you could actually look at individual genomes, they differ from the consensus. Conceptually this was totally unexpected at the time. We discovered this in 1976 and published it in 1977. I gave a seminar on our findings in a winter meeting in Klosters which Manfred Eigen had organized and he got very excited about them, because he had on theoretical grounds predicted that this is what one should find. He had even invented a name for it; he called this ensemble of particles a "quasi-species," but we didn't know his work because it wasn't published. These nucleotide variations come about, because in every round of replication the replicating enzyme makes mistakes. We could determine the error rate, which was about 10^{-4}. Once an error is made it is propagated in the next generation, along with some new error. At the same time there is also selection against viruses that become less viable as a result of these mutations. When particles accumulate too many errors, they replicate more slowly, so they get eliminated from the population. Finally, a steady-state equilibrium is reached. We once took a single particle with a mutation in it and propagated it for 20 generations: the resulting population was again a mixture of different individuals with the same consensus sequence we had started out with. This meant that after 20 generations we got the optimal population for the particular growth conditions we were subjecting the phage to.

Is this the same for the human DNA?

It is, and it was already known for humans by the name "polymorphism" but somehow nobody thought that viruses would have the same phenomenon. Esteban Domingo, my Spanish postdoc, continued working on this when he went back to Spain; he extended our work on RNA phages to animal RNA viruses. It turned out to be exactly the same thing for animal viruses, and recently it became extremely relevant because it was found to be the same for HIV. The reason AIDS patients rapidly get resistant to drugs is because they too have a quasi-population of virus particles. Within that population there may already be the particle with

resistance to a particular drug and it will multiply while the others will be suppressed. Thus 20 years later our chance observation with phages became essential to understand the biology of HIV. By then I was not working on it anymore.

Did people remember that you had started this?

Our work was published in *Cell.* It was quoted within the first few years but then it became part of the culture. Some people in the field still remember.

And Alzheimer's disease?

We were working mainly on prion diseases when we decided to make this PrP knockout mouse I already told you about. We had noted that these mice developed normally and remained healthy. It is, incidentally, quite likely that sheep and cattle devoid of the PrP gene would also be healthy and resistant to prion disease — it is being currently tried for sheep. I thought that if we could find a drug that diminished the production of PrP then you might achieve at least partial protection against the disease. For example, if someone is diagnosed at the early stage of Creutzfeldt-Jakob disease and you were to prevent the synthesis of PrP by a drug (which there isn't yet), then the PrP level would drop, the infectious agent would no longer reproduce and the disease should be stopped in its tracks. In Alzheimer's disease there is deposition of the Alzheimer peptide that forms amyloid plaques and many people believe that it is the deposition of amyloid that causes the damage in the brain. I thought that if you could delete the gene for PrP and nothing happens, maybe you can also delete the gene that makes the amyloid precursor protein, APP, without causing problems. That again would mean that one might develop a drug that prevents APP synthesis and arrests the progression of Alzheimer's disease. We developed APP knockout mice and these mice were normal for all practical purposes. Therefore, a strategy by which you could prevent or just diminish the synthesis of APP might be therapeutically useful. That was our involvement in the field. The next step would be up to a drug company and I haven't been successful in convincing one because it appears difficult to find a drug that would specifically inhibit the formation of one particular protein and not many others as well, and particularly a drug that would cross the brain-blood barrier. Also, I'm not so certain that if you don't make the peptide that you won't have the disease. The Alzheimer people are split on this issue. Some say that if you wouldn't

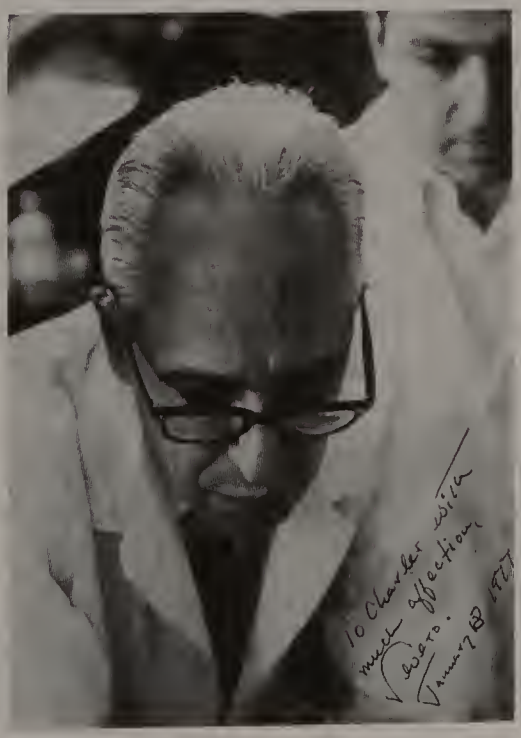
have the Alzheimer peptide, people would remain healthy. Others say that the amyloid peptide is only a consequence of the disease and if you eliminate it, you would still not stop the disease, you would only stop one aspect of it. Another reasonable strategy is to prevent the formation of the peptide. It arises by cleavage of the precursor protein APP that is partly embedded in the cell membrane. Then it is cleaved in two positions, about 40 amino acids apart and this internal peptide then forms the amyloid. One of the therapeutic approaches is to identify the enzymes that make the cleavages and to inhibit them. Then you would still be making the precursor but you wouldn't be making the peptide that forms the amyloid. This is the line the industry is following. It is intellectually reasonable because there is a lot of experience in how to inhibit enzymes.

You were at NYU, with Severo Ochoa, when Nirenberg initially cracked the genetic code. He announced it in Moscow in June 1961 ...

and I arrived in New York in October.

Was this a defeat for Ochoa?

The story is very interesting. It was an immensely important discovery. Experimentally it was trivial. At that time the concept of messenger had

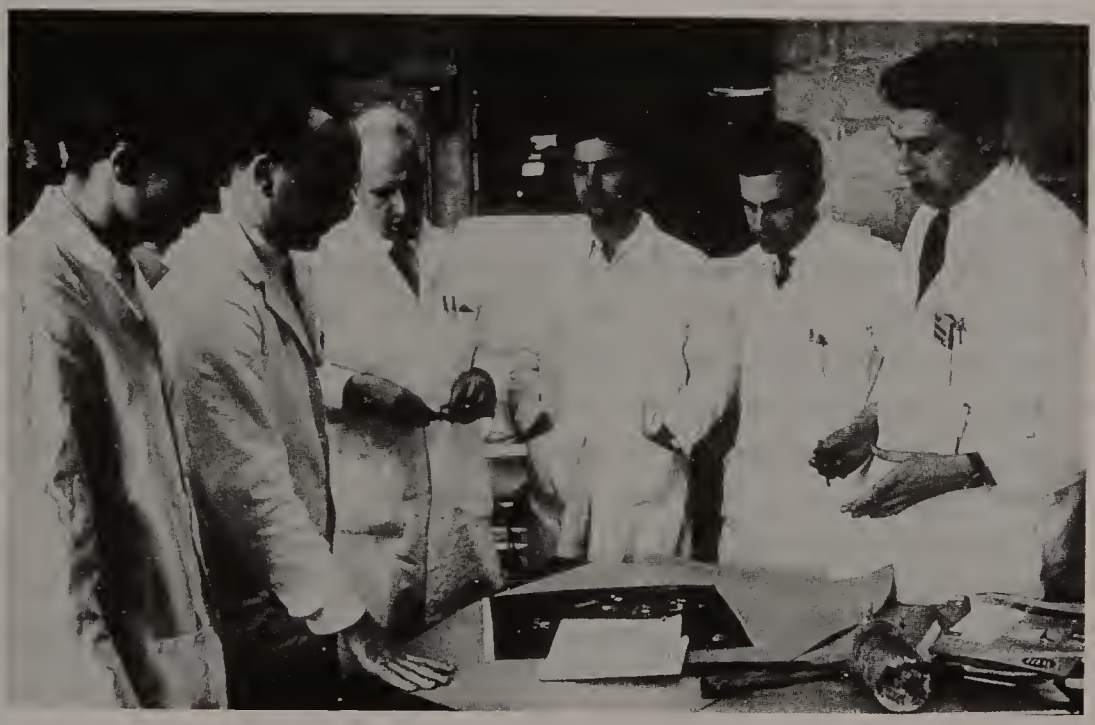


Severo Ochoa (1905–1993, Nobel Prize in Physiology or Medicine for 1959, courtesy of Charles Weissmann).

been developed, namely that ribosomes were programmed for protein synthesis by messenger RNA, or mRNA, which was the copy of a DNA gene. Many people wanted to take a specific RNA and elicit synthesis of a specific protein to prove the hypothesis. Nirenberg had the idea of using tobacco mosaic virus (TMV) RNA as mRNA for the coat protein of TMV. So he obtained TMV RNA from Heinz Fraenkel-Conrat, threw it into the cell-free protein synthesis system which he had developed and found that it stimulated incorporation of radioactive amino acids into protein, which is what you would expect from the messenger RNA hypothesis. But then he and Matthaei performed what was supposed to be a control experiment; at least that's the legend. It was to use an RNA or polynucleotide, which they expected would not code for anything, and show that it failed to stimulate protein synthesis. They chose poly(U). Let me digress here. Poly(U) is a polynucleotide that is made with an enzyme called polynucleotide phosphorylase. When you offer uridine diphosphate to polynucleotide phosphorylase, it just makes a chain of poly(U). If you offer it adenosine diphosphate, it makes a chain of poly A, and so on. The substrates of this enzyme are nucleoside diphosphates rather than triphosphates, as in the case of RNA or DNA polymerase. Polynucleotide phosphorylase was discovered by Ochoa who thought it was the enzyme responsible for RNA synthesis; in fact, it turned out to be an RNA degrading enzyme.

Anyway, one could use the enzyme to synthesize homopolymers by forcing the forward reaction with high concentrations of the substrate and Leon Heppel was making such polymers at the NIH. Nirenberg obtained some poly(U) from him, threw it into a protein-synthesizing reaction mixture, but instead of getting less, he got 20 times more incorporation than with TMV RNA. In these reaction all 20 amino acids were radioactive. In order to find out which amino acid was incorporated in the poly(U)-stimulated reaction, they performed 20 reactions using 19 amino acids and just one amino acid labeled at a time, and they found it was phenylalanine. From this they could conclude that if the code was a triplet code, then UUU was the triplet that coded for phenylalanine. Later they went on and found that poly C coded for polyproline; therefore, CCC was the triplet for proline. So that was Nirenberg's breakthrough.

In Ochoa's lab at the same time there was Peter Lengyel, whom I had already mentioned in the interferon story. He was a refugee from Hungary and became a graduate student in Ochoa's lab; he was and



In Ochoa's laboratory at New York University around 1963, from left, Piet Borst (later Professor and Director of the Dutch Cancer Institute), Ted Abbott, Severo Ochoa, Charles Weissmann, Martin Billeter (later Professor at the University of Zürich), Roy Burdon (Scotland, now retired) (courtesy of Charles Weissmann).

is an extremely smart person. Earlier that year, 1961, or even at the end of the previous year, he had the great idea of programming ribosomes with synthetic polynucleotides as messenger RNA. Lengyel was arguing from the beginning that something like poly(U) should code for a homopolypeptide. He presented this idea to some people and one of them was Charlie Gilvarg. Charlie is a brilliant biochemist, a biochemists' biochemist, with a very critical mind and very knowledgeable. He never achieved anything commensurate with his talents, but everything he did was elegant science; he did it *l'art pour l'art.* Lengyel explained him his idea and Charlie told him it would never work, because a polynucleotide, in order to be a messenger RNA, must have a signal indicating where translation has to start. If you have a series of nucleotides, there are three possible reading frames. You can start with 1, 2, 3; 1, 2, 3; etc., or you can start with 2, 3, 1; 2, 3, 1; or you can start with 3, 1, 2; 3, 1, 2; etc. Charlie said that the translation machinery must somehow determine what the reading frame is, where translation must start, and if UUU encodes an amino acid, poly(U)

cannot have such a signal because it consists of nothing but U residues. Lengyel, for this reason, and maybe because he was not insistent enough and didn't find much support in the lab, did not do his experiment. After Nirenberg's success, Lengyel was very upset but he immediately did the experiment with poly(U) and confirmed Nirenberg's conclusion that UUU must code for phenylalanine and CCC for proline. Then he went on in a very clever way to identify additional codons. GGG turned out to be glycine but it was technically difficult to do because poly(G) aggregates. Lengyel devised a strategy to define the composition of other codons. Thus he made a random copolymer with a ratio of U : C = 2:1 in which the triplets UUC, UCU or CUU were more frequent than CCU, CUC, or UCC, and a copolymer with the ratio U : C = 1:2 where the opposite was the case. He determined which of these polymers were better in incorporating particular amino acids. This way he could define the composition of the codons for many amino acids. Poly(A) was another interesting example. Poly(A) and A-rich copolymers did not seem to encode polypeptides and there was a lot of theorizing as to why nature abhorred A-rich mRNAs. Incorporation of a radioactive amino acid into a polypeptide was measured by adding trichloroacetic acid, which usually precipitated polypeptides while leaving amino acids in the supernatant. When you did that to measure proteins formed in response to poly(A) you didn't find any acid-precipitable product. A young graduate student, Gardner, did some reading and found out that some basic proteins were soluble in trichloroacetic acid but could be precipitated with phosphotungstic acid. The same night he carried out the experiment and by next morning he had discovered that poly(A) encoded polylysine and the codon for lysine was AAA. It is interesting that in Nirenberg's lab and Ochoa's lab dozens of people had failed to find out what poly(A) encoded because they apparently didn't know enough chemistry to realize that a polycation might form a soluble salt with a polyanion. I find this an interesting example of how sometimes a young inexperienced student finds the solution to a problem that eludes more experienced senior scientists.

Nirenberg's discovery was very important but it was also lucky for him that very important people in the field seem to have been waiting for this discovery.

By the end of the 1950s, Crick had come to the conclusion that the only way you could determine the code was by sequencing both a messenger

RNA and the protein it encoded, and then correlate each amino acid with a codon. Wittmann in Germany sequenced the coat protein of tobacco mosaic virus (TMV) and Fraenkel-Conrat had shown that the nucleic acid of TMV, which was an RNA, was responsible for coding for the coat protein. If it had been possible to sequence the gene for the coat protein one could have elucidated the genetic code . However, it was to take another fifteen years or so until this became technically possible. Nirenberg's rather simple approach turned out to be amazingly successful. In an article, I believe in 1961, Crick recounted how he heard Nirenberg's talk and he used the word thunderstruck or something similar to describe his reaction.

Why didn't other people do what Nirenberg did?

For one, they didn't have the biochemical system set up. This was a time when people were just starting to study cell-free protein synthesis. For this you had to have radioactive amino acids and these became available only quite some time after World War II. I remember when I got into the field in 1961, there were still people trying, in vain, to study protein synthesis without using radioactivity.

After Nirenberg's discovery became known, and it was only a step, however seminal, in cracking the genetic code, was there a race between Nirenberg and Ochoa?

That race was about who could correlate amino acids with triplets faster. Despite the fact that Nirenberg had broken the genetic code, as the event was called, Ochoa identified most of the triplets, but only in regard to composition, not the order of the nucleotides. Then came the question, how does one determine the order of nucleotides within a triplet encoding a particular amino acid? That was solved by a beautiful experiment done by Phil Leder, a young postdoc in Nirenberg's lab. He had a rather outlandish idea; he took individual trinucleotides, mixed them with ribosomes and determined which tRNA, labeled with its cognate radioactive amino acid, was bound to the ribosomes. For example, if you took AAG, incubated it with ribosomes and lysyl tRNA linked to radioactive lysine, the radioactive complex would be bound to the ribosomes, but any other tRNA, linked to its cognate radioactive amino acid, would not be bound. Conversely, AGA, or GAA would not mediate binding of lysyl

tRNA. To most of us it was unexpected that a trinucleotide could mediate binding of a tRNA because it was thought that hydrogen bonding between three base pairs would be insufficient to give stability. What we did not realize is that there is an entropic component here because both the triplet and the anticodon loop of the tRNA are held in a very specific conformation. Leder, probably being ignorant of all these problems, simply tried the experiment and it worked. So this final breakthrough also came in Nirenberg's lab and it was through Leder's work. With this approach they determined the sequence of all the triplets, with perhaps the exception of one or two. Then Khorana did the final, definitive assignments, but I won't go into that.

What was working with Ochoa like?

I spent seven years with him, first as a postdoc but by the time I left I had become Associate Professor. The time I spent with Ochoa was the most important and rewarding period of my development. Ochoa was a Spanish grandee, a person of impeccable manners, most of the time very self-restrained. When he liked somebody, he was wonderful. He was like a scientific father to me. After the first one or two papers he let me publish completely independently, without his name on the papers. He supplied me with graduate students, postdocs, and financial support. Ochoa's main interest at the time was the genetic code and the initiation of protein synthesis. He was a true biochemist; he was always interested in isolating and if possible, crystallizing protein factors, enzymes, and so on. He isolated the initiation factors of protein synthesis in *E. coli.*

For the poly(U) that didn't seem to be needed.

That's right, so why did the *in vitro* system work, both with natural and synthetic mRNAs? The protein synthesis systems used at the time were 20 millimolar or more in Mg^{++}, and at this level of Mg^{++} even poly(U) will attach to the ribosome precluding the need for initiation factors and an initiation signal (which was eventually identified as mostly being AUG). It is only when you go down to 4 mM, which is about the level in *E. coli*, that you require AUG and protein factors, and then initiation is specific. The reason poly(U) works as a messenger in the *in vitro* system is the artifactually high level of Mg^{++}.

Was it by accident?

People were trying to get *in vitro* protein synthesis to work in the absence of initiation factors, which were still unknown, and they found that they could get it to work with 20 millimolar Mg^{++}. They didn't realize that this was artifactual as regards initiation; they were just interested in getting protein synthesis. Interesting.

Was Ochoa a refugee?

He was a refugee by choice; he didn't want to live under the Franco regime in Spain. First he went to Germany, he studied there, then, with the outbreak of the war, he went to England, and later to St. Louis.

I would like to ask you about your beginnings, family background, education, the beginnings of your career.

My parents were living in Switzerland but I was born in 1931 in Budapest, while my mother was visiting with a friend. A few weeks after my birth my mother returned to Switzerland with me.

Little Charles in Hungarian folk costume (courtesy of Charles Weissmann).

I am Swiss, I grew up in Switzerland, except for four years when we were in Brazil during World War II. My father was worried that the Germans would occupy Switzerland and that the Swiss Jews would suffer the same fate as those in Germany. He was well advised to go, because it could have happened. My father was born in Rzeszow and moved to Switzerland before World War I, and my mother came from Lemberg, both Galician towns in Poland.

My father was in the film business, he had movie houses in Switzerland as early as 1912, when movies were still silent. One of them was in Zürich and was called Radium. My uncle, my mother's brother, accompanied the film on the piano. Then my father was associated with film production in Germany during the 1920s and early 1930s. One of the major successes was "Mayerling," with Charles Boyer. I saw the film a few years ago and didn't like it much; tastes change. In Brazil, my father didn't undertake much; he never learned the language; he was already 60 years old when we moved, and it was difficult for him. We came back to Switzerland in 1946 and he restarted his business, which was by then film distribution, and he distributed the films of Alexander Korda; the greatest success was "The Third Man," with Orson Welles. My father worked until he was 89, although he stopped buying new films when he was 85.

I got interested in science at the age of 11 when I read Paul de Kruif's book *Microbe Hunters*. I still see the cover picture in front of me, a picture of Paul Muni playing, I believe Robert Koch, in a movie. I read the book in English. I learned English when I was 4 years old; I was brought up by an English governess.

I early on wanted to become a physician and I took great interest in medicine already when I was 12 or 13 years old. I bought a lot of second hand textbooks on histology. I was fascinated by histology; I found it very aesthetic. My great wish was to have a microscope, but it was only when I was 16 that my father bought me an old Zeiss microscope. By then we were back in Switzerland. In Brazil, all I was doing was reading textbooks and copying drawings out of histology books. My parents sent me to a Brazilian rather than to an American or English school, as other refugee families did. None of the teachers spoke English, except for the English teacher, and I quickly became fluent in Portuguese. At home we spoke High German; my father never learned Swiss German.

My father was a rather observant Jew and I was brought up mildly observant. When I was about 22, I took my girl friend Sigi, who was to

Charles and Juliette Weissmann, London, 2000 (photograph by I. Hargittai).

become my first wife, on a car trip to the south of France. On one occasion we left all our belongings on the back seat of the car while we went shopping. By the time we returned, someone had reached in through the open window and stolen, of all things, the bag with my tefillin, that is, my phylacteries, but not my camera, which was next to it. I considered it as a sign that I didn't have to have lay tefillin anymore.

I have four children, one daughter, Ruth, from a premarital relationship when I was very young, and two boys, Jody and Ricki, and a girl, Susi, from my first wife Sigi. My current wife, Juliette, also has three children from her first marriage. Juliette and I have a long history; we were introduced to each other when she was seventeen and I twenty-six; it was an attempt at match-making by our families. We went out together for some two years but when I left for the U.S. in 1960, we separated and both she and I got married to others. We then met again in 1970, and fell in love. We eventually divorced our spouses and married.

While I was a medical student at the University of Zürich, I also had a laboratory in the attic of our home and was doing research on my own. I published two papers on work I did in this laboratory while I was a medical student. They had to do with vital staining using acridine orange. Later on I did some research in the Biochemistry Department of the University and I realized that with my training as a physician I would never really become a competent researcher. That is when I decided to

Paul Karrer (1889–1971, Nobel Prize in Chemistry for 1937, courtesy of Charles Weissmann).

study organic chemistry. I eventually became a graduate student — the last one — of Paul Karrer, the famous natural product chemist. He received the Nobel Prize in Chemistry in 1937 (shared with Walter Haworth) for his investigations on carotenoids, flavins and Vitamins A and B2. So, after my MD, I got a Ph.D. in organic chemistry. I loved chemistry, I enjoyed the manual work, crystallizing compounds and determining their structure. At the end of my work in Karrer's lab, I had to give him samples of the compounds I had made. I had made about 70 compounds and while sealing and labeling them I had occasion to think about where all this work had taken me and where it might lead me. I came to the conclusion that it wasn't going to lead me anywhere. I had the feeling that most of the really interesting synthetic work had been accomplished. It was Woodward's day — total synthesis of quinine, steroids, chlorophyll, colchicine; Vitamin B12 about to be done. Structural analysis was beginning to be performed by infrared and NMR spectroscopy, and by X-ray crystallography, and the techniques I had learned were going to be obsolete very quickly.

Then I heard a talk by Severo Ochoa. It was an inspiring talk. Ochoa was soon to receive the Nobel Prize for discovering an enzyme that he

thought was responsible for synthesizing RNA in the cell. By the time he got the Nobel Prize he must have already realized that this was not the natural function of polynucleotide phosphorylase. You could force it to synthesize RNA by reversing the reaction with high concentrations of nucleoside diphosphates; it was actually a degradative enzyme. Sam Weiss, Audrey Stevens, and Jerry Hurwitz then discovered the real enzyme, which was a DNA-dependent RNA polymerase and used nucleoside triphosphates as substrate. But anyway, Ochoa was a superb biochemist who did a lot of interesting work on oxidative phosphorylation, isolating and crystallizing many enzymes of intermediate metabolism, and so on. It was from Ochoa that I heard about modern nucleic acid biochemistry. It wasn't taught yet at the time in Switzerland and my textbook of biochemistry still said that DNA was probably a storage form of nucleotides. From Ochoa I got my first glimpse of the world of nucleic acids and proteins, and I decided to go to him to New York for my postdoctoral work.

In 1967, I returned to Switzerland where I became the Director of the newly established Institute of Molecular Biology at the University of Zürich.

You started life with financial freedom, which is rare among scientists. Then, later in your life you seemed to gravitate into moneymaking projects. Was it important to you?

I never believed my projects would make money. I joined the Biogen project because I thought it was an exciting adventure; I always had the desire to turn basic research into something practical. As a young student I dreamed of curing cancer. Inasmuch as interferon can be helpful in some cancer indications, I made a modest contribution in this direction. As it happens, I did also benefit financially and I have enjoyed building up a small art collection and sponsoring research through a foundation I set up some years ago.

Your path is different from many of the prominent figures of biotechnology today as you first got an MD then a Ph.D. because you wanted to become stronger in chemistry. Many of the leaders in biotechnology did not go through this classical training. What would you recommend for the next generation?

My training resulted in a broadened horizon, which led me to projects that I might otherwise not have pursued. I never considered my rather

time-consuming studies a waste of time. Today, there are combined MD/Ph.D. programs that can be completed more rapidly than I did.

If you could chart your career from the beginning, would you follow the same path that you did?

Yes; there are very few things, which I'd do differently. Of course, if I had the wisdom of hindsight, I wouldn't miss as many opportunities as I did; very often I had ideas and then I approached them in the wrong way or too slowly. Other than that, I would probably not have changed much. I only have one relatively small regret, maybe not so small, but I would've spent more time with my children. I almost never spent the summer vacations with my children because there was always a Cold Spring Harbor Meeting, a Gordon Conference, or some other meeting. Had I gone to one or two conferences less, I wouldn't have missed that much and I would have retained more memories with my children.

You have been very successful.

I failed in many projects. Many professors give a final lecture on their achievements when they retire; I was thinking of giving a lecture only about my failures, but it would have been too long. In the end I didn't give any lecture at all.

Altogether, I've had an exceedingly lucky life and interesting career; I have no regrets. When I set out to become a researcher, I felt very insecure and worried that I would fail. But somehow everything worked out quite well. I've also been quite healthy, at least so far. I sometimes wonder about my father. He was very successful in what he did, but in the last year of his life he was bedridden, paralyzed by a stroke. He was very aware but couldn't speak and much of the time he was dozing; sometimes he opened his eyes and I could see that he was completely conscious of what was going on around him. I never knew what he was thinking or what he wanted. I wonder whether he regretted his life because of the suffering in that final year. I will never know. I knew though that at the end he wanted to die because he refused to eat, he refused to drink, it was very clear.

Was he helped dying?

Not that I know of. When he refused food, the physician gave him infusions and that was another torture for him. My mother kept my father at home

Charles Weissmann in front of his father's image (courtesy of Charles Weissmann).

and cared for him day and night. He was the great love of her life and when he died she no longer had any interest to continue living, despite her children and grandchildren. I would not have had the courage to help my father die and I don't know whether his physician was humane enough to do so. I don't know.

Do you ever think of such an eventuality for yourself?

Yes. I have an agreement with a close friend; if either of us came into such a situation, we would not let each other suffer in that fashion.

Would there be legal complications?

If you were totally paralyzed and could not take a poison on your own, yes, but if you were able to take a glass and bring it to your lips, in Switzerland it's not a problem. Helping someone to commit suicide is not a crime.

I would like to ask you about your wife.

Juliette came out of Hungary with her parents in 1944 when she was very small. They were on that train to Switzerland with the group of Jews traded by the Germans for goods. She remembers very little and her mother died soon afterwards. Her father was a rabbi and although they were put in a camp first, she was allowed to go to attend school and her father became rabbi in Biel.

I have an aunt who was in a concentration camp, with a number on her arm, and for decades I never raised the subject because I thought that it would be a sore thing for her to talk about. Then I read this book *If This Is A Man* by Primo Levi and somewhere he says that rather than being reluctant, people want to talk about it. So after I'd read the book, next time when I went to New York where my aunt lives, she is 96 now, I asked her to tell me about her experience in the camp and how she had survived. She said, "Finally, you asked me!" This was after 50 years.

There were medical experiments in Auschwitz that we have known about, but few have known that Josef Mengele was doing his infamous crimes in Auschwitz under the auspices of the Deutsche Forschungsgemeinschaft.

I wasn't aware of this, but I do know that scientists in several of what are today Max Planck Institutes used human material that they obtained from Mengele.

How should the scientific community treat information from these human experiments?

That is a very interesting question and opinions diverge strongly. I'm probably in the minority here, but my view is that if valuable information had been obtained, obtained at the cost of the victims, and if this information could help others, it should be used, despite its criminal origin. If a member of my family had been a victim, I believe it would be some consolation if his suffering resulted in the saving of lives. The sad truth is that, as far as I know, nothing of value was discovered in those so-called "experiments."

There are still thousands of brains of people killed for studying their brains, stored somewhere in Germany.

I would consider it highly objectionable to use these brains for research. They should be buried. But with information recorded on paper, that's a different situation; it's not the same as continuing the experiment.

Why are these brains still being stored in Germany?

They should not be stored, they should not be used, they should be buried.

Could we end this conversation on a lighter note?

You have led me down paths I have not visited in decades; it has been an interesting experience and has given me food for much thought.

Frederick C. Robbins, 2000 (photograph by Magdolna Hargittai).

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Frederick C. Robbins

Frederick Chapman Robbins (b. 1916, Auburn, Alabama) is University Professor Emeritus at the Department of Epidemiology and Biostatistics of Case Western Reserve University (CWRU) and Dean Emeritus of CWRU School of Medicine. Together with John F. Enders and Thomas Weller, he received the 1954 Nobel Prize in Physiology or Medicine for "their development of techniques for the growth of poliovirus in cultures of non-nervous tissue." Their work paved the way to the development of the vaccines against poliomyelitis by Jonas Salk and Albert Sabin and eventually to the almost total eradication of polio from the entire world. He received his MD from Harvard Medical School in 1940. He served from 1942 until 1946 in the U.S. Army. He spent his residency at the Boston Children's Hospital, where the polio work was done. He became Professor of Pediatrics at WRU School of Medicine and Director of the Department of Pediatric and Contagious Diseases at Cleveland City Hospital in 1952, then Dean of the School of Medicine at CWRU in 1966. Dr. Robbins served as President of the Institute of Medicine of the National Academy of Sciences from 1980–1985. He is a Member of the National Academy of Sciences of the United States, the American Academy of Arts and Sciences, the American Philosophical Society, and many other learned societies. He has received numerous awards and honorary degrees and he has held positions in many committees especially on viral and other infectious diseases world-wide. Our conversation took place in his office at CWRU on October 4, 2000.*

*This interview was prepared by Magdolna Hargittai.

What turned you to science?

My father was a scientist, a botanist. I often worked in his laboratory as a boy, washing dishes. That did not really turn me on. Also, just like many young people I did not want to be just a copy of my father, I wanted to be myself.

I had first attended the University of Missouri Medical School but there was only a 2-year training there. Then I transferred to the Harvard Medical School. There I saw faculty members who were clinicians but they were also scientists — and that intrigued me. When I received my medical degree I went to the Children's Hospital for my post MD training; those of us who came directly from medical school had to spend a year in the laboratory. I was assigned to the bacteriology laboratory. Thus, when I went into the Army in 1942, I was assigned to laboratory service and given the responsibility for the Virus and Rickettsia Laboratory of the 15th General Medical Laboratory of the U.S. Army. Of course, I did not know much about viruses and very little about rickettsiae. I was sent to Italy where I stayed for two years. I did studies on Q-fever and hepatitis and that increased my interest in research and infectious diseases. When I came back from the war, I decided to do research and teaching.

I started to be interested in virology already a little earlier because my roommate in the fourth year of medical school, Tom Weller, chose to do elective work with Dr. John Enders who was studying viruses. Tom kept telling me about the interesting work they were doing and what a wonderful person Dr. Enders was, so that initiated my interest in viruses.

After the war, I completed my residency and then I joined Dr. Enders. I received a three-year fellowship and the original plan was that I spend the first year of that with Dr. Enders and two years with Dr. Macfarlane Burnet in Australia. Since at the end of the first year we started to get very interesting results on polio, Dr. Enders suggested that I not go to Australia but stay with him.

You wrote about Dr. Enders in the section Profiles in Pediatrics *in* The Journal of Pediatrics *that originally neither of you were really interested in polio because it was the "band-wagon topic" of the day. Why did you change your mind then?*

I started out to see if I could use tissue culture to cultivate a virus from infant diarrhea — those days infant diarrhea was a big problem. Dr. Weller,

Polio patients in "iron lungs." In some polio-stricken patients the disease paralyzed not only limbs but the muscles needed to breathe. The iron lung was a machine, which drew air into the chest; by doing so the body had to be isolated in a tank with the head outside while vacuum was created inside the tank (courtesy of Frederick Robbins).

who preceded me in Dr. Enders' laboratory, was trying to cultivate the virus of chickenpox. As I remember — Dr. Weller does not remember it quite that way — we were talking about the fact that polio was predominantly an infection of the intestines. Dr. Enders suggested that since we had some tissue cultures why don't we just put some polio in. So this is how it started.

So it was not by accident.

No, not by accident. Dr. Enders clearly saw the possibility. I was going to try tissue cultures of the intestines because, as we knew, polio grew in the intestines. Well, as it turned out, polio grew in almost any cell and the intestine was not important.

You make this sound so simple. But by that time there were already many people working on polio — that was the reason why you yourself did not want to join that "band-wagon." Then you started to work on it and you solved the problem within a year. What made the difference?

Actually, a few others had already tried tissue culture. Dr. Burnet had some suggestive results but he never pursued them. Dr. Sabin already had made an attempt to grow the poliovirus in human embryonic brain without success. He never figured out why it did not work, maybe he had the wrong virus strain. Maybe they just did not believe in them and did not pursue the work long enough. I became a believer when I saw that in the cultures infected with polio, the cells that were killed. We had a phenol red indicator in the medium. If the cells were alive and producing acid, the medium was yellow, and those that were not alive and not producing acid were red. I noticed the changes and it turned out that this was a very good indicator of whether the virus was growing or not. This was that convinced me.

Was it your earlier experience with tissue cultures that helped you or was this pure luck?

When I came to the laboratory in 1947, the first assignment that Dr. Enders gave me was to review the literature on viruses and tissue culture. There was some literature, even if they did not always use it the way we did. Reading the literature sort of sensitized me.

When you finally knew that you had the poliovirus growing in the tissue culture, why did you stop this work and why did not you develop the vaccine?

Dr. Enders thought that developing the vaccine was a kind of routine work once you had the techniques. He was more interested in looking into other viruses, such as measles and so on.

But for the measles he actually developed the vaccine.

Yes. I think he learned his lesson.

Weren't you or Dr. Weller interested in developing the polio vaccine?

Oh, Weller was very interested! He wanted to go ahead with the vaccine. I saw Dr. Enders' point. Our lab was small and doing that work would have meant scaling up quite a lot. Dr. Salk was already straining at the leash. In fact, Dr. Salk offered me a job. But it was pretty clear that anybody working in that lab was working for Dr. Salk and I was not particularly interested in that.

When you were seeing that you succeeded in growing the poliovirus in the tissue culture, did you know that this was a work of a Nobel Prize caliber?

No. We never thought that. When we eventually got the Prize we were surprised. A year before we got it, there was a rumor that we have been considered but we did not take it very seriously.

You wrote somewhere that Dr. Enders was very nice and he himself saw to it that his younger colleagues, Dr. Weller and yourself were also included in the Nobel Prize. What did you mean by that?

By the way the papers were published, he continuously gave credit to the two of us. Once a member of the Nobel Committee visited our lab. We did not know that that was why he was visiting, but Dr. Enders made it pretty clear that we were involved as his collaborators. He could have easily just not mentioned us and he could have ended up the sole recipient; after all he was the senior person in the lab and it was his lab.

Please, tell us more about him.

Dr. Enders was a very interesting man. He came from a very well to do background. His grandfather founded the Aetna Life Insurance Company in Hartford, Connecticut. He went to Yale as an undergraduate and was working for his Ph.D. in English literature at Harvard. He was living in a rooming house with a man from Australia, Hugh Ward, who was working for his Ph.D. at the Department of Bacteriology at the Medical School at Harvard. Dr. Enders decided that his studies in English literature were not going to do much good for the world and saw that what his roommate was doing in the laboratory was quite exciting, he changed subjects and took his Ph.D. in Bacteriology. The chairman of the Department at that time was Hans Zinsser, who was a charismatic and dynamic person — he actually had quite a bit of influence on me as well although I had not really known him. I think he also had an influence on Dr. Enders. Dr. Enders was at the Department of Bacteriology as a faculty member for a number of years and then his first wife died of influenza. He was at loose ends for a while and I am not sure why this came about, but he decided to move to Children's Hospital to establish a laboratory there. Dr Weller joined him right away and I came there a little later.

As a person he was very thoughtful, someone who very much enjoyed a high level conversation. In the laboratory we would have our lunch at a big table, not very sanitary but there it was; and the discussions ranged all over the place. I enjoyed this very much but Dr. Weller only occasionally joined us. This was quite an experience for me. Dr. Enders also liked to fish, I went with him a couple of times salmon-fishing in Canada. He liked his drink in the evening and to philosophize. He was a thoughtful and kind person. In those days many of the professors at Harvard Medical School who did research were independently wealthy. In fact, I was considering going into academic medicine and went to talk to one of my teachers, Dr. Gamble, whose family was the Gamble of Procter and Gamble. The first question he asked me was if I had independent means and I did not. He said he never would have been able to make it if he had not had independent means. I came along just at the time when fellowships became available from the National Institute of Health and others. The fellowship I received was actually money from the National Foundation for Infantile Paralysis and was administered by the National Research Council. So the field opened up just about then. For two years, I worked on the fellowship and then I went onto Dr. Ender's grant. All this was already after World War II.

Would you care to tell me something about Dr. Weller?

Dr. Weller's father was a Professor of Pathology at Michigan. Dr. Weller developed an interest in parasitology even when he was in college but in Medical School he did his elective studies with Dr. Enders. He was a well-organized, very intelligent person, even if a little stiff. He does not like to show emotion much and he and I are very different. But we got along very well and I have great admiration for him. He finally succeeded with the chickenpox, cultivated the tissue culture and now there is a vaccine against it which is, to a large extent, his work. It was a Japanese fellow, who actually produced the vaccine. Dr. Weller was the chairman of the Department of Tropical Public Health at Harvard for most of his career

At the Nobel award ceremony in Stockholm in 1954, from left to right, Linus Pauling (1901–1994, chemistry), the American Ambassador, substituting for Ernest Hemingway (literature), Thomas Weller (1915, physiology or medicine), Frederick Robbins (1916, physiology or medicine), John Enders (1897–1985, physiology or medicine), and Max Born (1882–1970, physics) (courtesy of Frederick Robbins).

and he is a devoted teacher. I think that he took the Nobel Prize more seriously than either Enders or I did. Dr. Enders looked a little as if he had walked into the wrong room. I myself felt a little that way but I don't think Dr. Weller felt that way. We were in Stockholm at the same time as Pauling and he certainly did not think that he was in the wrong room! The physicist, Max Born, was very quiet and he did not look as if he was very sure about it either. And, of course, Hemingway, the author, did not come.

Did not you realize the importance of your discovery? By that time polio was a terrible disease terrifying people every summer.

Sure, it was important and people were constantly coming to visit us. I was rather thinking that Salk would get the Prize. Although Sabin was more of a scientist than Salk but his vaccine came later.

Why did you think that Salk would get the Prize why not Sabin as well?

Sabin had not yet produced his vaccine at that time.

There was a serious disagreement between them after they had developed their different vaccines, Salk the inactivated one and Sabin the live, attenuated one.

They were fierce competitors. I don't know what else one can say. It got to the point, for instance, that when at the Institute of Medicine in Washington we had a session on polio and on the vaccine, we decided not to invite either of them so they were just asked to submit their contribution in writing. If they were both there we would have had a donnybrook and we did not want that. But I have a sneaking admiration for Sabin. He was a difficult man and had a tremendous ego but he was quite a good scientist. Salk also had a tremendous ego but, in my opinion, was less of a scientist.

Was money much involved?

I don't think that either of them got much money from it; neither of the vaccines was patented. It was just a matter of prestige and, of course, the National Foundation for Infantile Paralysis put up money for the Salk Institute. Although they did not get the Nobel Prize, both of them got

Jonas Salk (1914–1995) and Albert Sabin (1906–1993) (courtesy of Frederick Robbins).

a lot of prizes. They did not do badly. Salk divorced his first wife and married Picasso's girlfriend.

The large efficacy trial for the Salk vaccine was done in 1954 and when it was completed in 1955, the vaccine was licensed and began to be used. So it was difficult to do the trials of the Sabin vaccine in this country and thus he went over to Russia. The trials were conducted there and in some of the other Eastern European countries. Dr. Horstman from Yale went over there and reviewed the data and came back saying that the evidence was reasonable, and that was the basis for the licensing of the Sabin vaccine. We probably would not have eradicated polio in the Western Hemisphere if we had not had the oral vaccine. If you have to immunize everybody with a needle and syringe it is much more difficult to accomplish technically than just putting a few drops in a child's mouth.

Are you saying that the Sabin vaccine is better?

It is better for a number of reasons. First of all, it is much more easily distributed. It gives you better immunity of the intestine, which means

reducing dissemination. It is not as good from the point of view of reactions. About one in five hundred thousand children becomes paralyzed. That is why in this country now we are using the Salk vaccine.

Is every child getting the vaccine nowadays?

Supposed to, but you know the failings of the public health system ...

It was an important step when in 1993 polio was eradicated in the Americas. You write in the Polio *book that hopefully there would be a total worldwide eradication by the year 2000. Has it happened?*

No. There are too many countries in disruption. The People's Republic of the Congo, e.g., does not even have a government now, so this is difficult. Although India has put up a good fight they still have not totally succeeded. Then Afghanistan and some of the other countries are extremely difficult to deal with. I think if we succeed by 2003, we'll be doing well. However, a lot of countries are already free.

What is being done with those countries that still are not?

First, teams go to these places to help. In some countries they were even able to stop the war long enough to conduct the campaign. I was more involved with the work on this Hemisphere. Actually the "Shining Path," the rebels in Peru, even helped out. They saw the benefit to their people. It was more difficult in Central Africa, in places like the former Zaire, or Sierra Leone. They try in these countries to get National Immunization Days, when every child they can get their hands on is immunized; then they repeat it in a month. They also have to have a surveillance system, so that any child with an acute paralysis is investigated and if it turns out polio or suspect polio; then they saturate the entire neighborhood. They also have programs in which they go from house to house and immunize every child in every household. But to do that in places like Afghanistan is not easy.

There are sometimes people in religious sects who do not let their children immunized.

This has caused problems, like in Canada, for example. People in Holland did not get immunized and they brought polio to members of the same sect in Canada but this can be sealed off. Some of these sects have been

convinced and now they allow their children to get immunized. We have had no polio in the Western Hemisphere since 1994, when it was proclaimed that it was eradicated, and I think that now we are safe. However, we still have to immunize as long as poliovirus exists in the rest of the world. It is getting more and more difficult to convince people that this is important because they have never seen the disease, and this applies also to measles and mumps.

Is it still possible for an epidemic to break out?

Yes. Of course, the situation with smallpox is quite different. That is a fascinating problem, what to do with the stocks of smallpox in the freezers in Moscow and Atlanta. I was in favor of getting rid of them, but when you stop to think that we have no way of knowing whether Libya, for instance, has a stock of virus, or another, so-called "rogue" country and would, all of a sudden, distribute it. You have a population, which is like the American Indian; they never had the virus and were highly susceptible, they died like flies from smallpox. I think that some of our forbears even went as far as introduce contaminated blankets to the Indian villages — an early form of biological warfare.

Soon after the polio work you left Boston and came here, to Cleveland. Why?

I clearly was ready to take off on my own. This school at that time was in the process of developing a new curriculum, which was quite revolutionary and quite intriguing to me. Also, the position that I was offered was Director of Pediatrics and Contagious Diseases at what was then the City Hospital (now it is the County Hospital), where all the polios from this area were taken care of as well as other contagious diseases. That intrigued me. There were also a couple of people, among them Dr. Ramekhamp, whom I had known, who was interested in rheumatic fever, and we got along extremely well. He was a great attraction to me. The whole environment was very exciting.

Would you care to tell us something about your research here?

A lot of the research that we did here was more of a clinical and epidemiological research, we did studies on patients with polio-like diseases and showed that we could isolate other enteric viruses from them, not polio.

Frederick Robbins selecting slides for his forthcoming lecture, 2000 (photograph by Magdolna Hargittai).

We also did an antibody survey in the community, we tried to cultivate the rubella virus but did not succeed; others did. We were involved with the trials of the polio vaccine; we did studies on the response of newborns to the live vaccine. Merck produced a killed vaccine, which was much more potent, than the original. We agreed to give it a try and inoculated a hundred newborns with it. Then suddenly someone from Merck, Dr. Hilleman, called up and said: "I hope you have not given them that vaccine!" "Why?" "Because it is contaminated with SV40 virus!" SV40 is a virus that, at least in mice, causes tumors. It is latent in monkey kidneys. When you cultivate these monkey kidney cells, the virus is reactivated. So a lot of people received SV40 virus and there is some evidence now, even if not necessarily solid,

but suggestive evidence, that some tumors of the brain in people is the result of this SV40. They are still trying to document this.

Was this anybody's fault?

No. Nobody knew that it was there. Dr. Morrimer, who is my associate down the hall, has been involved with the studies of whether SV40 does any harm or not. We did 20 years follow-up of the infants, and did not find any evidence but now it is 40 years, and god knows ...

Have you been involved with teaching?

I have always enjoyed teaching and came here largely because of the new curriculum. I still do a little teaching but not much. In 1966, I became Dean of the School and that put an end to my research.

When you took up the Deanship, it must have been obvious that you would not be able to do as much research as previously. Why did you do it?

Well, the main reason was that a lot of faculty were pushing me to do it. There was a concern that if I did not, someone else would be appointed who would not be favorably inclined towards the curriculum; I had several people in my laboratory and every year had to worry about how to get the grants to support that large group, I was getting tired of it. All the same, I did not really want to do the Deanship, if truth be known; so to some extent it was a sacrifice. But I was always very devoted to the school.

What was your major achievement as Dean?

Oh, dear. Preserving the remnants of the curriculum. The major thing I feel best about is that we were able to turn things around and increase the enrollment of women and minorities. We had one of the best records in minorities; for example, 3 years ago the entering class had 53 percent women. Of course, we don't know how many of them will actually become doctors and have a career; our society is not set up to make it easy for them.

Would you mind telling us something about your wife?

She was Dr. Weller's technician, that is how we met. She graduated from Vassar College and grew up in Princeton. Her father in 1946 took a little

trip to Stockholm.[1] After we had our first child, she gave up her career and has been a devoted and affectionate mother. We have two children, two fine young women.

What do they do?

One married a young man who is now a Professor of Music at St. Olaf College in Minnesota, he teaches composition and theory and does a fair amount of composing, some of his things have been commissioned. They don't have any children. She is very much involved with the environmental movement and works for an organization, called "Save the Canon-River Valley." Our younger daughter is not married; she just got her Ph.D. in the History of Science and probably is going to get a job as an editor. They both are very interested in the environment.

How much interaction did you have with John Northrop, your father-in-law?

A fair amount. We often went fishing together. He was a great fisherman and bird hunter. He was a very interesting man; he did not like to talk shop. When he was not in the laboratory, he wanted to talk about other things. His friends were people who liked to do the kind of things that he did. He was a superb athlete; he played tennis and golf very well. They had two children, my wife and her brother, who went into oceanography but is retired by now.

Dr. Northrop was an extraordinarily intelligent man. He had some interesting ideas about the early DNA stuff. He had been more oriented towards protein and protein replication; which today in the prion era is interesting. It took him a while to accept the new genetics, but he did. He also enjoyed his drink before dinner, he and I often shared it — I was a great admirer of his.

Do you know Carleton Gajdusek? I am asking because you brought up protein replication.

I know him very well. He worked for two years in our lab. He is brilliant. One of the few geniuses I have ever known. I could kick him for letting himself

[1]Mrs. Robbins' father is the late Professor John Northrop (1891–1987), who received the Nobel Prize in Chemistry in 1946 sharing half the prize with Wendell Stanley (1904–1971) "for their preparation of enzymes and virus proteins in a pure form." The other half went to James Sumner (1887–1955) "for his discovery that enzymes can be crystallized."

getting into the position he is in. We were good friends but since he has left the country I have not heard from him. It is truly tragic what happened. We stayed in his house along with his collection of Southern Pacific kids. I have never known anybody quite like him. I don't know what he thinks now but he was long far from being convinced that the prion business is right; I suppose that he is convinced now. I am very fond of him; he sent me everything he wrote, up until recently.

Did you know Paul de Kruif?

No, but he worked for my father-in-law.

Have you read his book, Microbe Hunters*? This book had an enormous impact in peoples' choosing careers in science.*

I was somewhat influenced by some of those books, *Arrowsmith*, *Microbe Hunters*, and the writings of Hans Zinsser.

Did the Nobel Prize change your life?

Yes, it did change, because everybody started to expect things of me that I could not deliver. One of the local science writers from a local paper here, for example, came to me about six months after the prize and asked, "What have you done now?" There was another strange outcome that I cannot quite explain. From the day of the announcement I never got a request to see a patient in consultation. The Prize also meant that I was more in demand for various committees and that sort; so it was somewhat distracting. To some extent it increased my own pressure and expectation of myself. For a certain length of time I was very disappointed in my own performance but finally I adjusted to it.

Have you had any contact with Drs. Enders and Weller after you left Boston?

Oh, sure. Mostly with Dr. Enders. He had a place up at the Connecticut shore, and we visited him there. I was very fond of him and I think he was fond of me. I had less interaction with Tom; he was in a different area, in the tropical disease area. Dr. Enders' second wife was the secretary in the lab; she was a widow with a son, a very lively, enthusiastic lady, we all liked her very much. She turned out to be a very good wife for him

(she died in 2000). Dr. Enders' son died quite a few years ago but there is a daughter, who lives in the Hartford area, Sally. She also went with us to Stockholm. We all went on a ship; Dr. Enders did not like flying. He had been in the Air Corps in World War I as an instructor, and he said that those airplanes that time were extremely hazardous to fly, so he felt that he has used up all his luck in the air. Tom Weller and his wife flew over but we went by ship, on Queen Elizabeth travelling first class and had a wonderful time.

Who are your heroes?

I guess Dr. Enders would be one. Dr. James Gamble would we another one, he was on the faculty at the Children's Hospital in Boston. I already mentioned him before, he was a very remarkable, fine man. I really came to know him pretty well. Gamble was extremely good with young people. So I think Enders, Gamble, and my father are the three heroes in my life.

Are you also good with young people?

I guess; fairly; as a teacher I have been reasonably successful; I am not so good with really young people, although as a pediatrician, I should be.

What was the greatest challenge in your life?

I guess; the Nobel Prize.

What will be your legacy?

Oh, heavens! My students and my children are the main ones and I guess the work we did is also something of a legacy. I enjoy very much observing the students whom I taught, what they are now doing in the world, it is very nice to see that.

Did you take up any causes or have you been approached by different organizations to help?

Oh, yes, although I have been very busy, I have not been able to do too much. But my wife and myself tried to support Planned Parenthood. I feel very strongly about that issue. Our whole family is quite committed to environmental issues, to the whole idea of conservation. I have also

been involved with drug policy that has largely to do with getting away from incarcerating people, instead of giving them a proper treatment. But I must admit, I have not been as active with it as I would have liked. I have been quite involved with the effort to immunize people and with the eradication campaigns. Politically not particularly; I am basically a liberal, I guess being an academic I can afford it. It is fascinating that Dr. Enders when I first knew him, he was very conservative; he grew up in a conservative business environment. As he got older he got more liberal and I am doing somewhat the same thing.

What is your relationship with religion?

I am not at all interested in organized religion. Some of the things churches do I am for; such as open doors for youngsters after school, to keep them occupied; I am all for that. But as a scientist I am not interested in formal religion and I am very annoyed by the Pope.

What other interests you have beside science?

We have a place in Maine where we go up in the summer; I like hiking and sailing. We have two acres there, so there is quite a lot to do outdoors. I used to like tennis, in recent years I took up golf because my wife likes it. I do a lot of reading, including mysteries. My wife and I enjoy music very much and we have an excellent symphony here, so we go there a lot.

Do you participate much in public life?

I have been involved with all sorts of things; but right now I am not so involved, I am trying to cut back. I have been involved with a lot of international organizations in recent years, helping get programs started in Uganda, India, etc., with vaccine action programs. I am on the committee that reviews the eradication status of polio for WHO. I am also on the Caribbean Health Research Council, and other committees but I am trying to cut back on various things. I am in a group whose task is to oversee the development of a malaria vaccine.

How do you see the principal difference between research done fifty years ago and today?

Well, fifty years ago it was quite a different kettle of fish. Now it is all molecular biology. It was beginning to be that way already before I left

and I did not think that I would be very competitive in that arena. But what people can do today is just incredible! Tissue culture today is nothing, ancient stuff, just routine.

But they still don't have vaccines for all kinds of diseases.

No, and molecular biology has not solved all our problems yet. TB, HIV, and malaria are the three biggies and all three of them are very difficult. I have been somewhat involved with HIV and malaria, and they are very complicated. Although molecular biology has offered approaches, it still has not totally solved these problems. And we still have to go to the field to test them.

If you started your career today what area would you like to work in?

I still would like to work with infectious diseases.

What do you think about the interaction between chemistry, biology, and the medical sciences?

I think they are still more separated than they should be. I am afraid that universities, at least in this country, tend to be set up to make it difficult to do interdisciplinary research. Each department is a sort of kingdom to itself and the way the funding stream is does not benefit work with other groups. We definitely have to figure out better ways to handle this. But there are some good signs; for example, our new professor of biochemistry is also an MD and I see him bringing chemistry and medicine together in a very desirable way. Generally, however, this is still a big problem. I even wrote a letter to the President of the University about this. I did not even get an answer. If I were to go back to research I would have to take some courses.

What are, in your opinion, the most important unsolved scientific problems today?

Obviously cancer. Cancer is a complicated problem because it involves molecular biology, it involves biology, it involves genetics, it involves environmental issues, so it is a complicated issue. Another such issue is raising children in the modern world, to be responsible citizens; that is also a problem we have not solved yet.

Looking back to the last 50 years, what was the most important scientific discovery in your opinion?

Obviously the double helix by Watson and Crick, antibiotics, and what we have learned about the function of the nervous system.

What do you anticipate in the next 50 years?

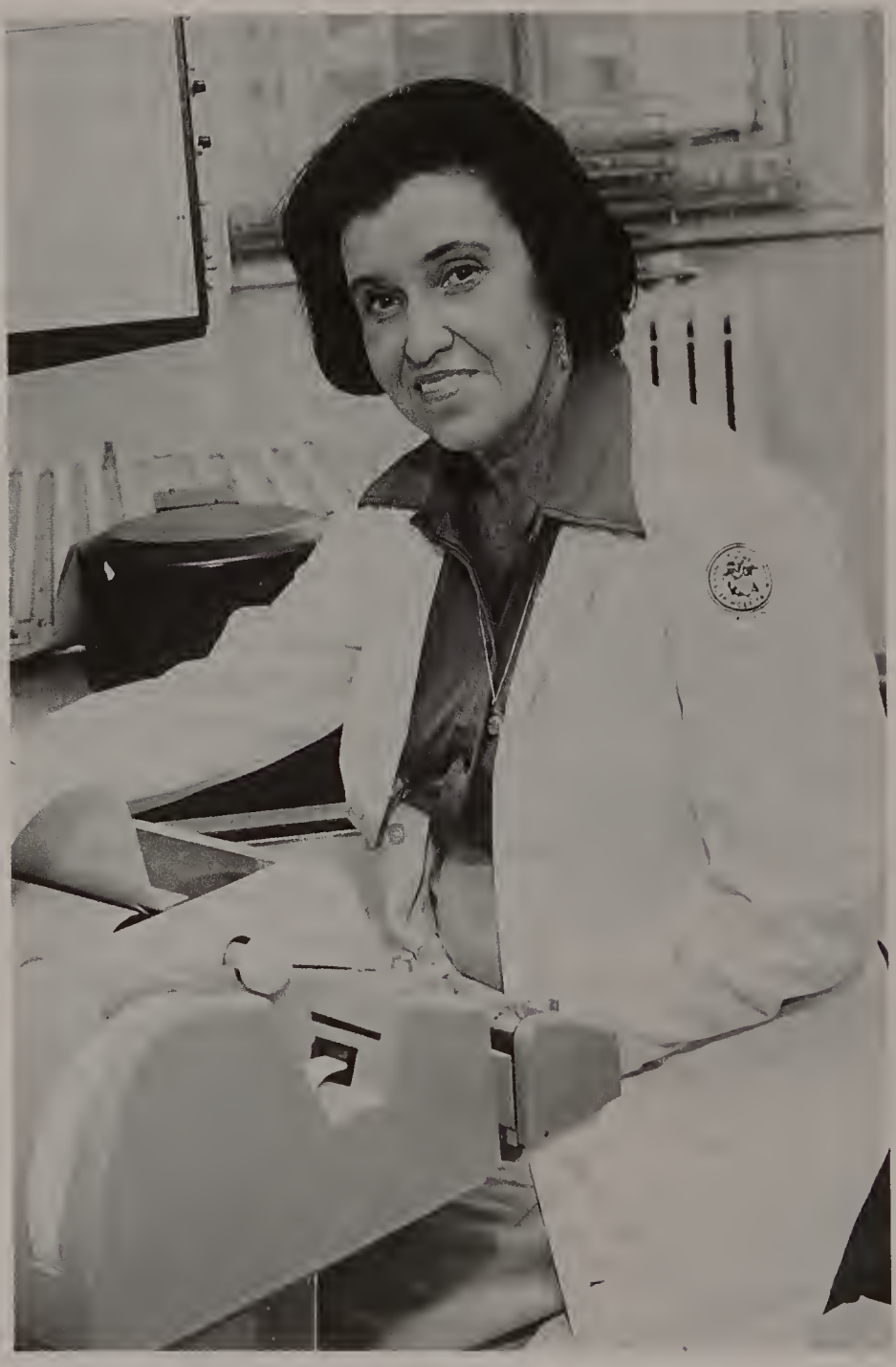
The whole issue of what we are going to do with the genome and its sequence. And I swear I am not entirely sure how we are going to use it. It is certainly very involved with ethical questions and I am not sure that some of the propaganda that is being distributed has been helpful. I think it is going to be more difficult than some people would like to admit, to apply it. It is a very complicated business.

Molecular biology is said to be the science of the second part of the 20th century. What will be the science of the next 50 years?

I think that molecular biology is going to dominate for quite a long time. Everybody says it is going to be the brain, neurobiology, but it is moving slowly. For some time to come I think molecular biology is going to be the dominant one.

Is there anything else I should have asked and have not?

I think that you have bled me dry.



Rosalyn Yalow (courtesy of Rosalyn Yalow).

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Rosalyn Yalow

Rosalyn Yalow (born Sussman, in 1921, in New York) received an A.B. in physics and chemistry from Hunter College in 1941 and an M.S. (1942) and Ph.D. (1945) in Nuclear Physics from the University of Illinois at Urbana. She worked for decades at the Bronx Veterans Administration Medical Center (VAMC); her last position was as Senior Medical Investigator and Director of the Solomon A. Berson Research Laboratory. She became Emeritus in 1992.

Dr. Yalow received the Nobel Prize in Physiology or Medicine in 1977 "for the development of radioimmunoassays [RIA] of peptide hormones." Her other distinctions include membership of the National Academy of Sciences of the United States, the National Medal of Science (1988), numerous other awards, memberships, and honorary doctorates.*

Rosalyn Yalow's seminal discovery, which was a joint work with the late Solomon A. Berson (1918–1972), is explained by Eugene Straus in his book [*Rosalyn Yalow, Nobel Laureate: Her Life and Work in Medicine*, Plenum, New York, 1998] in the following way:

"RIA — Berson and Yalow's crowning glory — is simple in principle. The concentration of the unknown unlabeled antigen, such as the insulin in your blood, is obtained by studying your blood's ability to displace the binding of radioactively labeled insulin to insulin-binding antibody. We compare the ability of a small quantity of your blood to inhibit the binding of insulin-^{131}I to insulin binding antibody with the inhibitory effect of known standards. Thus if a small volume of your

*This interview, in a shortened form, was originally published as part of a book review in *The Chemical Intelligencer* **1998**, *4*(4), 61–63 © 1998, Springer-Verlag, New York, Inc.

blood inhibits the binding of radioactive insulin to antibody to the same extent as 10 picograms of a standard insulin preparation obtained from a manufacturer, then your little sample of blood contained 10 picograms of insulin.

"The most remarkable thing about RIA is its sensitivity. It can measure unbelievably low concentrations of all sorts of substances. This sensitivity is essential for the measurement of peptide hormones because they circulate in the blood at incredibly low concentrations. And the RIA method has all of the specificity inherent in the precise reaction of an antigen with its specific antibody. The insulin antibody will find and bind and measure only the insulin among the myriad substances, many in billionfold higher concentrations, which are present in your blood sample. It is also inexpensive to do, and it is nearly as easy and quick to assay thousands of samples as just one or two. RIA was a breakthrough approach."

Eugene Straus is a Professor of Medicine at the State University of New York Health Science Center at Brooklyn, and worked for many years with Rosalyn Yalow. His book is dedicated to the memory of Bernard Straus, Eugene's father, the former chief of medicine of the Bronx VAMC. Bernard Straus helped bring together the Berson-Yalow partnership in 1951. Eventually, Berson suggested, shortly before his premature death, that Straus join Rosalyn Yalow. Yalow's health has deteriorated during the past few years and her struggles to overcome the consequences of ruthless strokes is described beautifully in the book by Straus. Solomon Berson left the Veterans Administration after two decades of the most vibrant and fruitful research relationship with Yalow and found himself in an impossible situation. As head of a big medical department, he was in confrontation with a president-dean who was anti-research and whose idol was a Nazi doctor who had performed experiments on victims in Dachau.

I visited Rosalyn Yalow on March 10, 1998. When I went to see her in her office at the Bronx VAMC, I did not know about her strokes, nor about this superb documentation of her life by Eugene Straus; the book was to come out in a few months time. Dr. Yalow received me graciously and told me about her career, especially about its beginnings.

My mother was 4 when her family came to this country and my father was born in New York. They both came from poor East European immigrant families. She completed the sixth grade and he the forth grade only, so they didn't even have the advantage of a high school education. But they were determined for their children to have a college education.

I went to school in the Bronx. It was not a great school but we had good teachers and the pupils were very motivated. They were predominantly poor and Jewish. I went to Hunter College, which was part of the New York City College system. The boys went to City College and the girls went to Hunter College.

I was very lucky. There were three physics professors at Hunter who took me under their wings, and I couldn't have imagined anything else for myself than becoming a physicist. It wasn't easy but eventually I was offered a teaching assistantship at the University of Illinois at Urbana. They brought in three Jews at Urbana that year, two boys in addition to myself. One of them was my future husband, Aaron Yalow. My thesis director was Maurice Goldhaber, who was later to become the Director of the Brookhaven National Laboratories.

The war made it possible for me and for many other young Jewish students to enter graduate school. While in Europe the Jews were being killed, the war made all the difference for Jews and for women in America.

I did my graduate research in nuclear physics. This was very much the thing to do at that time. After receiving my Ph.D., I did some teaching at Hunter and, eventually, I became an associate of the Bronx Veterans Administration. This place used to be much larger than it is now. It used

Rosalyn Yalow in the laboratory (courtesy of Rosalyn Yalow).

to have 1200 beds, and now there are about 500. The war veterans are dying off, and many of the surviving veterans go to small private hospitals.

My husband died five years ago, but we had a wonderful marriage. He was always very supportive. He was Professor of Physics at Cooper Union College here in New York. He was engaged in teaching, not research. We have two children. When they were small, in the 1950s, my mother used to come to help us with the children. We also had maids, first a sleep-in maid, later a part-time maid. They were wonderful, bright black women from the South. They came to New York, and they couldn't go to study, so they found work as maids. This made it possible for me to carry on with my job. For me, this was a very fortunate situation. Today this would be impossible.

Our daughter, Elanna, studied educational psychology and has her Ph.D. She lives in San Francisco, has two children, and works all over the country, setting up day-care centers. Our son, Benjamin, used to do computer work. He doesn't have a formal job currently. I live together with him. I've had three strokes, I have difficulties in moving my right hand, and my right leg is partially paralyzed. I come to my office regularly though, read my mail, keep up with things around me.

Your famous discovery, the radioimmunoassay technique, has been widely used. In view of today's commercial successes of biomedical discoveries, it is remarkable that you didn't patent it.

Solomon Berson and Rosalyn Yalow (courtesy of Rosalyn Yalow).

Rosalyn Yalow during the interview, 1998 (photograph by I. Hargittai).

This was a conscious decision on our part. The radioimmunoassay technique was a joint discovery by myself and Solomon A. Berson. Sol and I worked together for 18 years before he left the Veterans Administration and became Chairman of Medicine at the Mount Sinai School of Medicine in 1968. He died four years later. In 1972, a young MD, Eugene Straus joined me.

When Sol and I discovered the radioimmunoassay technique, at the beginning it had a slow start, but we knew it would catch up quickly because it was a very sensitive and very useful tool. We were very determined not to take out a patent on it but to do everything to help it spread. We organized courses to teach physicians to use the technique.

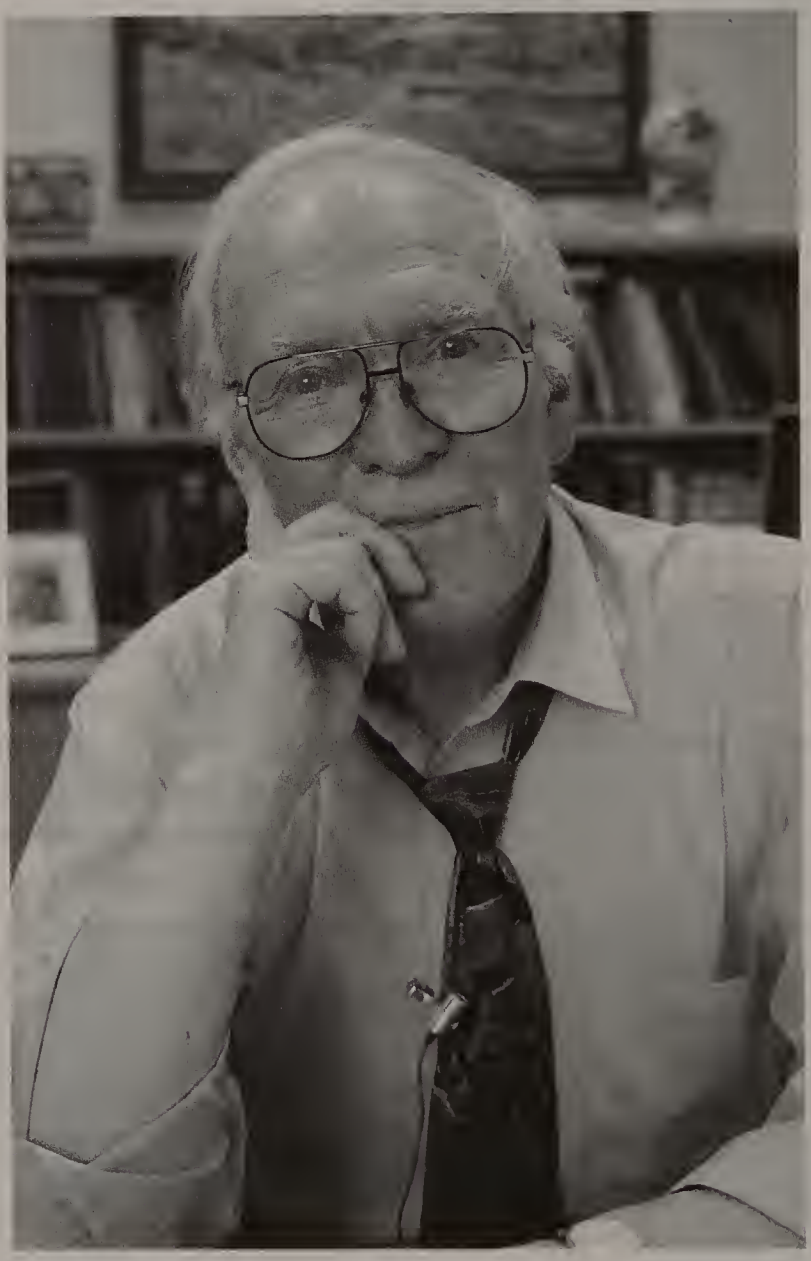
Sol and I made a great team. For many years we shared the same office. We had two desks in the office, and we were discussing things all the time. I never had any formal training in biology. He taught me everything I needed in biology and medicine, and I taught him some physics. He knew a lot of physics but he was an MD. Compared with a university setting, we had the great advantage of having no competition between us.

People who have written about you often use the word "tough" in describing you.

I did my job.

Any message for today's young women?

Study!



James W. Black, 1998 (photograph by I. Hargittai).

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James W. Black

James W. Black (b. 1924 in Uddingston, Scotland, U.K.) is Chairman of the James Black Foundation and Emeritus Professor of Analytical Pharmacology, King's College School of Medicine, London. He shared the 1988 Nobel Prize in Physiology or Medicine with Gertrude B. Elion and George H. Hitchings, both of the Wellcome Research Laboratories, Research Triangle Park, North Carolina, "for their discoveries of important principles for drug treatment."

James Black received his MB.ChB. degree from the University of St. Andrews in 1946. He spent periods of time in academia (St. Andrews University, University of Malaya, University of Glasgow, University College London, and King's College School of Medicine, London) and in pharmaceutical research and development (Imperial Chemical Industries; Smith, Kline & French Laboratories and the Wellcome Foundation Research Laboratories). Professor Black was elected Fellow of the Royal Society (London) in 1976, and awarded its Mullard Medal in 1978. He received the Wolf Prize in Medicine (Israel) in 1982, was elected Foreign Associate to the National Academy of Sciences of the United States in 1991, and was knighted in 1981 for his services to medical research. In 2000, he was awarded the Order of Merit of the United Kingdom whose membership is restricted to 24.

This narrative is based on a conversation recorded in Professor Black's office at the James Black Foundation in London on October 12, 1998. He corrected it in November 2000.

The James Black Foundation has been around for 12 years. Its goal is to make new drugs and new tools for making drugs. The Foundation is James Black's tribute to the memory of Sir Henry Wellcome. After Wellcome had become the sole owner of the Burroughs Wellcome Company Ltd., in 1924, he consolidated all his holdings into the Wellcome Foundation. On his death in 1936, his Will directed that all his corporate shares should be vested in a charity, the Wellcome Trust. So the Foundation's profits went to the Trust that was given the responsibility of funding curiosity-driven research, which was one of Sir Henry's major passions. Researchers who worked for the Wellcome Foundation loved this idea. But when all the Trust's equity was eventually sold to Glaxo, this unique mutual but independent interaction between industrial and academic research came to an end. Like the Wellcome Foundation, the James Black Foundation is a not-for-profit organization and any royalties that it may earn will pass to a Trust with the fiduciary duty of funding curiosity-driven biomedical research. The Foundation is statutorily limited to 20 scientists plus 4 in administration (a laboratory administrator, a storekeeper and two secretaries).

Mail box sign of the James Black Foundation in London (photograph by I. Hargittai).

Of the scientists, one is in charge of chemistry, another of pharmacology, and beyond that there is no administrative hierarchy. The Foundation contracts out all tasks for which a contract can be specified beforehand. These functions include patenting, financial affairs, legal advice, toxicity testing, large-scale synthetic chemistry and quality control. This avoids hassles that are typical of big companies. Black and his younger colleagues believe that there is no need to be big to discover drugs.

Before remembering the past, he quotes a cautionary note by Hilary Mantel (from a review of Attwood's novel *Alias Grace*): "Perhaps there is no such thing as memory, only the process of remembering. The product of memory is reconstruction, not reproduction."

He started day-dreaming when he was a little boy and it has continued ever since. It is directed day-dreaming in that he is thinking about problems. There were five boys in his family and he was the second from the bottom so he learned his place in life. There were a lot of influences in their home on character. His father was a mining engineer who had begun working as a coal miner when he was 12 and used night classes to advance his career.

James Black's intellectual awakening began at Cowdenbeath Secondary School, his local mining community's main school for higher education. He came under the influence of Dr. Waterson, the senior mathematics teacher in the school. Waterson, like Black, had grown up in the culture of the East Fife coal fields. Education, leading to self-improvement and escape from the dangers of mining, was the most important cultural activity in that community. Dr. Waterson grew up there and went to St. Andrews University in Fife to study mathematics. He was a brilliant student but did not take up a career in academic research, for which he was ideally suited, because he was programmed by his upbringing to become a schoolteacher. Remarkably, he earned his Ph.D. and then a scholarly D.Sc. while still a full-time schoolmaster.

When Black was 14, Dr. Waterson gave him a copy of *Calculus Made Easy* by Sylvanus P. Thompson to work through on his own. The answers to problems were at the back of the book. More than halfway through the sections on integral calculus, Black got a different answer to a problem from the one in book. He asked Dr. Waterson for help. The big man sat down beside him and worked through the problem at great speed. The teacher got the same answer as the pupil. The teacher's response was astonishing. "The book is wrong," he said, "I can do calculus as well

as Sylvanus P. Thompson." How could anyone have the knowledge and the confidence to challenge the authority of a book! This was Black's epiphany and he has been irreverent in his thinking ever since.

Waterson persuaded him to sit the Scholarship Examination for St. Andrews University and, at 16, James Black was offered a residential scholarship. He graduated in Medicine in 1946. While he enjoyed doctoring, he was antagonized by the hubris of the doctors who had taught him. The Science of Medicine, the Theory of Physic, was what really excited him. So, in 1946, he started a career in Physiology at the Medical School in Dundee.

Robert Garry was the Professor of Physiology. He had been working for many years on the motility and absorptive activity of the alimentary tract. When Black joined the Physiology Department, Garry was trying to find out how the intestine absorbed sugars selectively. Verzaar, a Swiss physiologist, argued that selective absorption of sugars followed from their selective phosphorylation in the intestinal epithelium. A major plank in his argument was that sodium iodoacetate, a known inhibitor of phosphorylating enzymes, abolished the selective absorption of sugars. Garry, however, showed that sodium iodoacetate destroyed the intestinal epithelium and argued that phosphorylation of sugars was not the explanation for selective absorption. Black's first encounter with a physiological research laboratory was to ask questions about anything and everything. So he wanted to know about other physiological effects of sodium iodoacetate. For example, did this enzyme poison interfere with the blood flow to the intestines, a possible rate-limiting step in absorption? If the poison interfered with blood flow to the gut, surely this would interfere with blood pressure. To find out, he developed a new technology to allow him to measure, continuously, the blood pressure of anaesthetized rats. He was able to show that sodium iodacetate dramatically and permanently lowered the blood pressure of these animals. This prompted a lot of questions in his mind about whether blood flow could be a rate-limiting factor in intestinal absorption. Black's whole scientific life since then has been in the physiology and pharmacology of the cardiovascular and alimentary systems, although he never got a satisfactory answer to his original question.

In 1947, he married Hilary Vaughan, a fellow student. In order to pay off his student debts, he accepted an appointment, in 1947, as Lecturer in Physiology at the Medical School in Singapore, then a British colony. He taught and did research in physiology. He made new equipment for measuring blood pressure and blood flow so he could study the pressure-flow relations of the intestinal circulation. In retrospect, the work was

excessively ambitious in relation to his experience. Although he got a lot of results, he found it hard to judge their value. He had nobody to talk to about his work. He oscillated between thinking, "this is great" and "this is rubbish." He learned there the tremendous importance of contacts with colleagues, how absolutely vital it is to normalize one's intellectual activity.

The Blacks returned to London in 1950 and he had a briefcase full of notes about his experiments. He was growing desperate in trying to find a job until, by chance, he ran into Professor Garry in Oxford Street in London. While Black had been abroad, Professor Garry had been appointed to the Regius Chair of Physiology at Glasgow. The University of Glasgow had just established a new Faculty of Veterinary Medicine led by a brilliant veterinarian, William (later Sir William) Weipers. Black was introduced to Weipers by Professor Garry and was very excited when he was offered the appointment of Lecturer in Veterinary Physiology. In his new Department, there was enough money to support his research without having to write grant applications. He was very much into developing his cardiovascular experiments and was able to buy a new multi-channel recorder and high performance manometers, but he had still to build flow-meters by his own hands. He soon managed to start two research collaborations with his new University colleagues. With Adam Smith, a gastroenterologist, he studied the inhibitory effects of 5-hydroxytryptamine (5-HT) on histamine-stimulated gastric acid secretion. In the early 1950s, 5-HT was very much a hot research topic. This work was to become very important, later on, to his work on histamine antagonists. The other collaborator, George Smith, was a cardiac surgeon at the University Hospital. Smith had been to the United States to learn the latest surgical techniques for trying to relieve the effects of coronary disease. All of these techniques were designed to engineer a collateral blood supply to the heart. However, Smith had also worked with Donald Gregg, a physiologist, who had shown that when a major coronary artery is closed there is a small retrograde flow, from the other coronary arteries, into the infarcted region. Nevertheless, this small flow is not enough to prevent the hypoxic ventricular muscle from developing fibrillation, a fatal arrhythmia. But, more importantly, Gregg had also shown that if this small retrograde flow could merely be doubled, then this would be enough to prevent the onset of fibrillation. Smith then reasoned that if such a small increase of blood flow could do that, then a small increase in the amount of oxygen carried in the retrograde supply should also be effective. So, back

home, Black introduced him to the new Veterinary Medical School. Smith put anaesthetized dogs into a high-pressure chamber with two-atmosphere pressure of pure oxygen and showed that this procedure did indeed greatly reduce the incidence of fibrillation after coronary artery occlusion. The technology of hyperbaric oxygen could, of course, never have become mainline medicine. So, Black, impressed by Smith's results, reasoned in the following way. At one fifth of an atmosphere of oxygen, the normal pressure in the air that we breathe, hemoglobin is 100 percent saturated. When you go to ten times that pressure, all you do is increase the amount of dissolved oxygen. But, oxygen is not very soluble in water. So hyperbaric oxygen only increases the oxygen-carrying capacity of blood by a few percent. He argued that if such a small increase in oxygen supply was life saving, then an equally small decrease in the heart's demand for oxygen should also be effective.

Once he got this idea, he found many other relevant findings in the literature. Thus, at one time, surgical removal of part of the thyroid had been used to relieve angina, the pain brought on by exercise in coronary artery disease. The removal of the thyroid reduces the heart rate and thus reduces the cardiac demand for oxygen. However, the angina is relieved only for a short time. Thyroid removal raises the blood cholesterol level and this speeds up the arterial degeneration. In a couple of years the patient is worse off than before the operation so this is why this procedure fell into disrepute.

Could the heart rate be reduced in any other way? Heart rate is mainly determined by the activity of the sympathetic nerves that supply the heart and by the levels of adrenaline in the blood. Drugs that block the actions of adrenaline, the antiadrenaline drugs, had been available for some years. However, patients treated with antiadrenaline drugs were known to get dizzy when they stood up, due to a rapid fall in blood pressure, and at the same time there was an embarrassing increase in heart rate. Both of these effects would be very undesirable in patients with angina. Presumably, this is why these drugs had never been tested in patients with angina.

So, was the concept of blocking the actions of adrenaline on the heart a bad idea? Black found the answer by accident. He had bought a copy of Drill's *Pharmacology in Medicine*, first published in 1954. In it was a chapter on adrenergic drugs written by Raymond Ahlquist. The story behind Ahlquist's chapter is an interesting commentary on scientific

prejudice. Isoprenaline, a close analogue of adrenaline, acts like adrenaline to increase heart rate and dilate the bronchi but, whereas adrenaline raises blood pressure, isoprenaline profoundly lowers blood pressure. To explain these phenomena, Ahlquist came up with the hypothesis that there are two kinds of adrenaline receptors in the cardiovascular system. He proposed that α-receptors are found in blood vessels and, when stimulated, produce vasoconstriction and a rise in blood pressure. On the other hand, he proposed that β-receptors are found in the heart as well as in blood vessels and, when stimulated, produce both an increase in heart rate and dilatation of blood vessels, which leads to the fall in blood pressure. This hypothesis elegantly explained both the effects of isoprenaline and the antiadrenaline drugs. Isoprenaline was proposed to be a selective stimulant of β-receptors and he classified the antiadrenaline drugs of the day as selective antagonists of α-receptors. This hypothesis was too revolutionary to be readily accepted by his contemporaries. On the one hand, this hypothesis contradicted the prevailing concept advanced by Walter Cannon, one of the doyens of American physiology. Cannon had explained the diversity of adrenaline's actions by proposing that two hypothetical substances were released in the tissues, Sympathin E (for the excitatory effects) and Sympathin I (for the inhibitory effects). Thus a hypothesis of two transmitters was being opposed by a hypothesis of two receptors. The other problem at that time was that physiologists did not believe in receptors. Although the idea that drugs acted on "receptors" was quite an old one, the idea was mainly used by pharmacologists as a theoretical concept to allow them to make mathematical models of drug-receptor interactions. No one had ever used the "receptor" concept to explain physiological phenomena. So, in the prevailing prejudices, he simply could not find any journal prepared to publish his work. Finally, when William Hamilton, his friend and colleague, became Editor of the *American Journal of Physiology*, his seminal work was published in 1948. But, to crown it all, his work was ignored for another 10 years. In the meantime, Ahlquist was given the chance to expound his ideas in Drill's multi-author textbook.

When Black read Ahlquist's chapters in Drill's book, he immediately realized that, to test his ideas about reducing cardiac oxygen demands, what he needed to do was to find a drug that would block the β-receptors in the heart. However, his colleagues were skeptical. Black's generation of doctors were imbued with the ideas that Walter Cannon had expounded

in a physiological textbook, the *Wisdom of the Body*. The central concept was that the whole of the autonomic nervous system is adapted to give the best physiological response to life's emergencies, the fight, flight and fright situations. In other words, at any moment, the heart rate, and hence its oxygen consumption, should be nicely matched to the oxygen needs of the tissues. If you reduced the demand for oxygen by reducing heart rate, then you would embarrass the heart by its failure to meet the oxygen needs of peripheral tissues. However, Black argued that, while this might be true for trained athletes (who have very low resting heart rates) he thought this would not be true for unfit people, including people with coronary artery disease. If a man is resting and then gets a fright, his heart rate will go shooting up and yet he is not doing any more work. The heart is pumping blood faster through the capillary circulation so that there is less time for oxygen to be extracted by the tissues, that is, the arterial-venous oxygen difference gets smaller. On the other hand, if his heart rate is too high and his pulse rate is then slowed, the blood will go more slowly through the capillaries and the arterial-venous oxygen difference will increase which is energetically free. That was the basis for the β-blocking story.

When Black asked ICI for support, he was visited in Glasgow by two senior ICI scientists. One of them was Dr. Garnet Davey, the Biological Research Director. Black was subsequently offered and accepted a senior scientist post in their new, custom-built, laboratories in Cheshire, just south of Manchester. In retrospect, he could see that his was an idiosyncratic appointment that had been powered through by Dr. Davey. At ICI, Davey became Black's constant champion in the face of a great deal of skepticism from the other pharmacologists about the whole β-receptor blocking concept. Nevertheless, he was given a young chemist, John Stephenson, and a technician and they started the β-blocking programme in 1958. They started with isoprenaline.

They knew that isoprenaline was a selective β-receptor stimulant and the structure of isoprenaline was their only clue. They thought that if N-substitution of adrenaline with an isopropyl group produced a selective agonist, then perhaps N-substitution with a much larger alkyl group might produce a compound that would selectively lose the ability to activate receptors but still bind to the receptors and block access to adrenaline. They called their target compound a β-receptor antagonist. Adrenaline and isoprenaline belong to the chemical class known as catecholamines. Making

analogues and derivatives of such compounds was not easy. Progress was slow. Then they learned about dichloroisoprenaline(DCI).

Isoprenaline is a bronchodilator with potential therapeutic use for treating asthma. However, it is also very short acting. Medicinal chemists at the Eli Lilly Corporation wanted to make a longer-lasting analogue. The hydroxyl groups on the catechol ring were notorious for being attacked metabolically so they replaced the hydroxyl groups with chlorine atoms in the hope that this would produce a compound that would be metabolically more stable. Alas, it turned out to be inactive as a bronchodilator. However, they noticed that when bronchial tissue was subsequently challenged with isoprenaline its relaxant effects were blocked. However, they did not appreciate at the time that what they had produced was a kind of β-receptor antagonist. As soon as Black saw that paper, early in 1959, he had no difficulty in persuading Stephenson to synthesize some DCI. When they tested DCI in their guinea-pig heart preparation it was as though they had added isoprenaline. DCI turned out to be a powerful stimulant of heart rate. This was not what they were looking for! Months later, Black developed a new bioassay, the papillary muscle from the inside of the left ventricle of the guinea-pig heart. This tissue is about 2–3 millimeters long and half a millimeter wide. This piece of muscle does not beat spontaneously; it needs to be stimulated. In this way, when the frequency of contraction is controlled, the force of contraction can be measured unambiguously. He could test both old and new compounds for their ability to block the inotropic (contraction-increasing effects) of adrenaline or isoprenaline. When he retested some older compounds, he found, to his surprise, that DCI did not stimulate the papillary muscle at all but, on the contrary, it blocked the effects of adrenaline. Black did not understand that he had, in fact, exposed a potent partial agonist, a pharmacological property that had only recently been understood although in a different chemical class. Stephenson was quick to suggest that he would replace the dichloro-phenyl ring of DCI with the isosteric naphthyl ring, a compound later known as pronethalol. Pronethalol turned out to have none of DCI's stimulant actions on the heart but was able to block the stimulant actions of adrenaline. This was the first, so-called, "beta-blocker".

As Black had speculated, beta-receptor blockade reduced the exercise performance of trained athletes but improved the performance of people who were physically unfit, especially including patients with

exercise-induced angina. However, he had failed to anticipate that beta-blockers would also become major drugs for the treatment of hypertension. This is a class action, which, he believes, is the result of ironing out the exercise and emotion induced increments in heart rate. Over a 24 hour period, this has the effect of marginally reducing blood pressure averaged over a full day. Average blood pressure is the load on the muscle cells in heart and blood vessels that stimulates them to grow bigger and stronger, the ultimate "cause" of high blood pressure. So beta-blockers reverse this trend and gradually reduce blood pressure over a period of several months.

While doing this work he had gradually learned that there were pharmacological parallels between histamine and adrenaline. During his work with Adam Smith at the Veterinary School in Glasgow, he had learned that, although histamine was a powerful stimulant of acid secretion in the stomach, the so-called anti-histamine drugs were known to be unable to inhibit that secretion. Daniel Bovet, a medicinal chemist working in Fourneau's laboratory in Paris in the 1930s, had previously been impressed by the chemical parallels between histamine and adrenaline. Chemically, both substances were derived from the decarboxylation of natural amino acids and both were substituted ethylamines. Fourneau had already found a series of aryl-ethylamines that had anti-adrenaline properties. Bovet then showed that some of Fourneau's compounds could also block the effects of histamine on bronchial muscle. He went on to synthesize highly selective histamine antagonists, work for which he was awarded the Nobel Prize in 1957. However, it became clear during World War II that the new antihistamines did not block histamine-stimulated acid secretion. Hence the parallelism. Fourneau's anti-adrenaline drugs blocked Ahlquist's α-receptors but not Ahlquist's β-receptors. Bovet's anti-histamines blocked the histamine equivalent of Ahlquist's α-receptors but there were no drugs known that would block the histamine-equivalent of Ahlquist's β-receptors. Black saw very clearly that what he wanted to find was an antagonist of histamine's "β-receptors." The scientific problem was clear. However, the commercial problem was confused. Understandably, ICI wanted to use Black's scientific understanding of the new clinical pharmacology about physiological receptors and their various agonists, partial agonists and antagonists that interacted with them. However, Black had no enthusiasm for the commercial development of the beta-blockers and decided to follow

Edward Paget, one of his ICI colleagues, to Smith, Kline & French Laboratories at Welwyn Garden City in Herts. The deal was that Black would be allowed to develop his ideas about inventing a "histamine β-receptor" antagonist of histamine-stimulated gastric acid secretion. He tried to follow the same pathway he had used at ICI. He set up a bioassay for histamine-stimulated acid secretion in anaesthetized rats — the so-called Ghosh and Schild preparation. His chemists synthesized analogues of histamine. Each compound was tested for its histamine-like agonist activity and then for its ability, if any, to inhibit histamine-stimulated acid secretion. His game plan was to use the same chemical strategy that had been so successful with adrenaline. In the adrenaline series, selective agonist activity appeared when the side chain was modified (the isopropyl analogue of adrenaline, isoprenaline) and selective antagonists were developed by modifying the heterocyclic end of the molecule. Black and his chemical colleagues (brilliantly led by Robin Ganellin) set out to do the same exercise on histamine. They intended to concentrate their synthetic efforts on modifying the imidazole ring of histamine. The chemistry was difficult. So, at the beginning they made what they could. The ninth compound they made, the side chain substitution of the amino group with the guanidine group (GAH), appeared to be an agonist like histamine so it was ignored. Then, as a synthetic exercise, the chemists substituted a methyl group in every possible position of the histamine molecule. The early excitement came when they found that 4-methyl-histamine (4-MeH) was to gastric secretion what DCI was to the heart — a highly selective agonist at histamine's "β-receptors." So, the clues that he had overdone the parallelism between adrenaline and histamine were there early in the programme but Black misread them. In fact, it took three years before Black realized that compound 9 was to histamine what DCI was to adrenaline — a partial agonist. The whole strategy had to be switched. Unlike adrenaline antagonists, histamine β-receptor antagonists would come from modifying the sidechain. Once they realized this, the antagonists burimamide, metiamide and cimetidine followed soon afterwards. They were named histamine H_2-receptor antagonists because Ash and Schild had recently classified the receptors blocked by Bovet's antihistamines as H_1-receptors. The pharmacological theories at that time could not explain why the effects of partial agonists are tissue-dependent. Some years later, he and Paul Leff developed an operational model of agonist and partial agonists that explained his findings with both DCI and GAH. In fact, the deliberate search for partial

agonists is now part of his game plan. That is basically the story of the histamine H_2-receptor antagonists (blockers) that have proved very effective in the treatment of peptic ulcers.

Essentially, Black used the same strategy in the invention of the β-blockers and the H_2-receptor antagonists. First, there was no wishful thinking. Both of his targets were clearly defined by physiological hormone-receptor interactions. In each case, the physiological interaction specified the appropriate bioassays to detect the pharmacological action that he was seeking. Moreover, the chemistry of the hormones, adrenaline and histamine, gave the medicinal chemists clear directions — start here! Before he started these projects he was able to foresee how he would be able to confirm animal-derived laboratory pharmacology in man. Finally, in each case, he had a disease in mind that he would want to investigate with his new compounds. In neither case did he know whether the new compound would be therapeutically effective — pronethalol and burimamide were exploratory tools. He knew that, at the very least, these compounds, prototype drugs, would help clinicians to answer important physiological questions. He never promised his sponsors more than that. However, we now know that, in the end, the sponsors' faith allowed them to make a great deal of money.

Black is continuing to use the old strategies and tactics in his pursuit of new drugs. They are still working for him but the slow pace of his current projects frustrates him. Is there an alternative approach? All of the major pharmaceutical companies believe there is. They have made a huge investment of capital and faith in supporting the development of combinatorial chemistry (combichem), with associated chemical libraries, gene banks and search engines. The huge chemical libraries are then evaluated with the technology of high-throughput-screening (HTS). Combinatorial chemistry covers a wide range of techniques that permits chemical building blocks, such as amino acids, nucleotides or small organic reactive fragments to combine randomly. Huge numbers of compounds can be made extremely quickly. The technology for screening these compounds very rapidly (HTS) has been developed at the same time. Cells from animal tissues can now be programmed to express human proteins, enzymes as well as membrane-bound receptors. These cells, or even the pure proteins extracted from them linked to beads of resin, can now be exposed to thousands of ligands at one time to provide the high-through-put assays. Combichem plus HTS is now the dominant driving force in pharmaceutical research. This has been going on for nearly 10 years with the expectation that this strategy

will produce new drugs faster. However, so far, the expectations have not quite materialized. Should we be concerned about this? Are the new technologies based on, and limited by, wishful thinking, an attitude that he regards as equivalent to original sin in new drug research? The new technologies are designed to generate "hits" and "leads." But Black is not convinced that finding starter molecules is the rate-limiting step in new drug discovery.

His second concern is that the new methods are predicated on the assumption that the new drugs are going to be like the old drugs. The drugs that Black has developed have interfered with command-control processes in physiology. In an emergency, adrenaline gives the heart a command; there is no option, adrenaline instructs the heart to "beat faster." Similarly, when you eat, histamine is released and gives the stomach the command "secret acid." These messenger-driven processes are inherently reversible. For example, the exercise-induced increase in heart rate readily reverses when the exercise ceases. Antagonists of command-control messenger molecules have turned out to be very effective medicines.

We are now learning that some of the more complicated and interesting biological processes may be controlled in a different way. Processes such as commitment of stem cells, activation of T-cell lymphocytes, sprouting of new capillaries, the inflammatory process and so are inherently irreversible. Once initiated there is no way back. However, if any of these processes are initiated inappropriately, the consequences are pathological. How then are these processes controlled so they are only activated when the response is appropriate to physiological need. An interesting feature of these processes is that many different messenger molecules can influence them. He imagines that reliable activation occurs only when a number of different molecules, from different cellular sources, arrive simultaneously at the target cell to deliver subliminal stimuli that potentiate each other. This would be the chemical equivalent of a neural network. Drugs that block only one of these molecular events might turn out to be clinically disappointing. We have got to go beyond molecular biology into integrated physiology, to understand how the systems are organized and controlled, and find the rate controlling pathways. Enzymologists have known this for years.

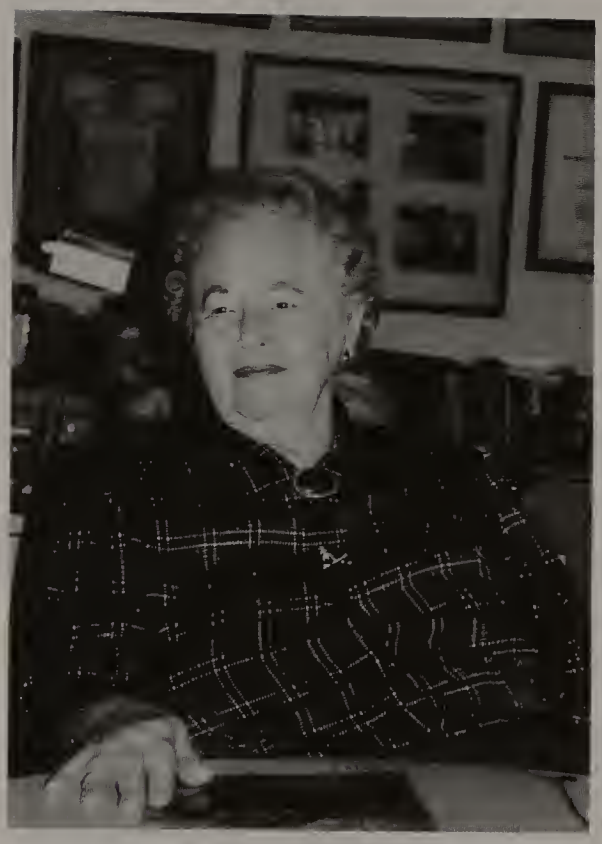
Black says that if he could start all over again, he would learn more maths and study chemotaxis as a convergently-controlled system. He thinks that that would be both rewarding and exciting.

The Nobel Prize in Physiology and Medicine for 1988 was awarded jointly to Sir James W. Black, Gertrude B. Elion, and George H. Hitchings "for their discoveries of important principles for drug treatment." I recorded a conversation with Gertrude Elion in 1996; it was included in the inaugurating volume of the *Candid Science* series (*Conversations with Famous Chemists*, ICP, London, **2000**, Ch. 5, pp. 54–71). After that recording I stayed in correspondence with Dr. Elion and at one point I asked her to put together something on George Hitchings about whom she had spoken so beautifully in our conversation and who had died earlier in 1998.

Dr. Elion promised to collect some photographs and in her letter of November 16, 1998, she told me about her busy schedule, "... I have been traveling a great deal giving lectures and attending meetings and never seem to get caught up with my other obligations. I will, however, try to collect some photographs for you, as you suggested. ... I am having cataract surgery tomorrow and will probably not be doing much in the office for the next two weeks. I will try to get the pictures soon ..."

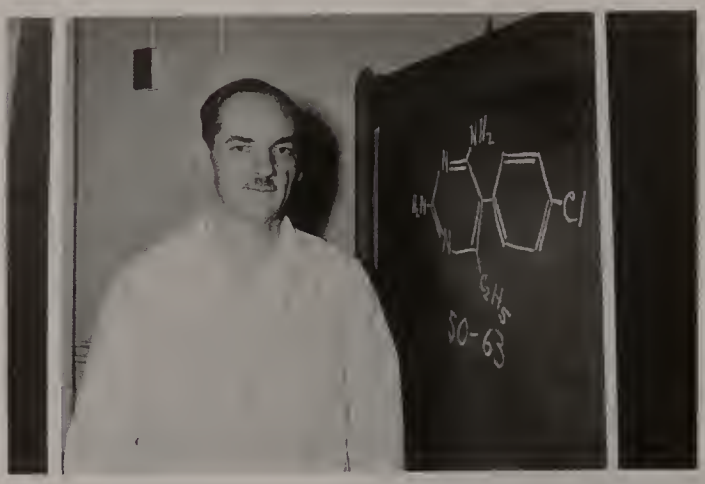
On February 2, 1999 not only did she report on her successful cataract operation but by then she had been through a trip to Europe. She was making progress in the compilation of photographs and in doing so, she enlisted the help of the son, Thomas, and daughter-in-law, Kathy Bendo, of George Hitchings.

On February 17, Dr. Elion sent me some pictures with some commentaries, which are used in the captions here. In the meantime I had sent her photocopies of images Kathy Bendo had sent me and I asked Dr. Elion about two of them in particular. One showed her with George Hitchings and someone else walking on the Atlantic City boardwalk and the other showed George Hitchings in a sport team from 1923. She responded in a letter dated February 19 and her response is excerpted in the respective captions. Her letter arrived in Wilmington, North Carolina, where I was at that time, on Monday, February 22, the same day I learned that Gertrude Elion died on Sunday, February 21.



Gertrude Elion in 1996 (photograph by I. Hargittai). Gertrude Elion (GE) wrote me in 1998, "This is the best picture of me that has been taken in the past 15 years."

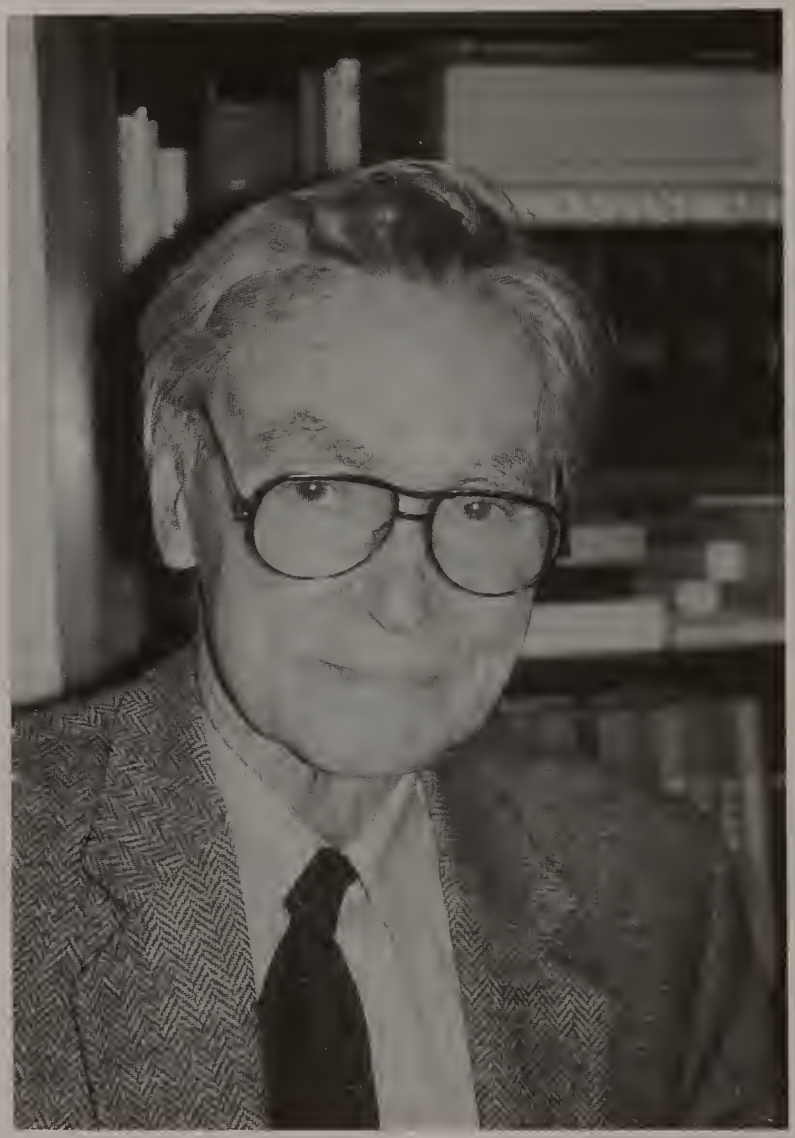
George Hitchings and Gertrude Elion shortly after the announcement of their Nobel Prize. Photograph and © by Will and Denny McIntyre, Greensboro, North Carolina; reproduced with permission.



GE: "George Hitchings in the laboratory in Tuckahoe in the 1950s. The formula for 50-63 is that of Daraprim (pyrmethamine), the antimalarial, 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine" (courtesy of Gertrude Elion).

GE: "George [Hitchings] walking on the Atlantic City boardwalk with me and another woman, Doris Lorz. This was in 1956 on the occasion of the Spring meeting of the Federation of American Societies for Experimental Biology. Doris Lorz was working at Burroughs Wellcome at that time, studying substrates and inhibitors of xanthine oxidase. She was the one who discovered the inhibiting activity of allopurinol on that enzyme" (courtesy of Kathy Bendo).

George Hitchings (second from the top and second from the left) in a track team in 1923 (courtesy of Kathy Bendo). GE (in response to my question): "Your comment about the integrated sport team is interesting. I believe that college sports in a state university in the Northwest, as this one, the University of Washington in Seattle, would have been integrated in 1923."



K. Sune D. Bergström, 1999 (photography by I. Hargittai).

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K. Sune D. Bergström

K. Sune D. Bergström (b. 1916 in Stockholm, Sweden) is Professor Emeritus of the Karolinska Institute in Stockholm. He shared the Nobel Prize in Physiology or Medicine in 1982 with Bengt I. Samuelsson and John Vane "for their discoveries concerning prostaglandins and related biologically active substances." Our conversation was recorded in Professor Bergström's home in Stockholm on October 16, 1999, and I summarize below what he told me.

Sune Bergström's father was a mathematician and died in the Spanish flu at the age of 29 years when Sune was three. His mother was a schoolteacher and was left alone with three children. Her life was a struggle and she never remarried. Her father was a medical doctor and there was a long association back in medicine on her side. Sune's brother became a teacher and his sister became a librarian. Bengström was already a professor when his mother died. He married his wife in 1942, upon his return from America. She was a laboratory technician at the Karolinska. They have one son who is in the computer business.

Bergström's entry into science was accidental. He had jumped half a year in school and got out around New Year and the medical school was the only one that he could start right away. He had planned to go into the Institute of Technology and had taken mathematics before that. There were no entrance examinations in his time; the students just signed up for a school. His first teacher was a very stimulating Finnish chemistry docent, Dr. Erik Jorpes. Jorpes worked on heparin so Bergström worked also on

heparin for a couple of years. Jorpes was also a pioneer in getting blood transfusion into the clinic. He had royalty income from heparin and he spent some of that money to send Bergström to study in London. Among his heroes, Bergström also mentions Hugo Theorell as a brilliant person.

Sune Bergström got both his Dr. Med. Sci. and MD degrees in 1944 at the Karolinska Institute. Following various shorter-term appointments, he spent ten years, between 1947–1958 as Professor of Physiological Chemistry at the University of Lund. Since 1958, his career was at the Karolinska Institute. He had many administrative and science policy appointments; among others, he was Rector of the Karolinska Institute (1969–1977), Chairman of the Board of Directors of the Nobel Foundation (1975–1987), and President of the Royal Swedish Academy of Sciences (1983–1985). He has been a Member of the Royal Swedish Academy of Sciences since 1965, of the National Academy of Sciences (Washington, DC) since 1973, the Academy of Sciences of the USSR since 1976, and the Pontifical Academy of Sciences since 1986, just to mention a few such distinctions. He received the Gairdner Award in 1972, the Albert Lasker Basic Medical Research Award in 1977, and the Robert Welch Award (Texas) in 1980, among many others.

When I asked Professor Bergström about the beginning of his career, he told me that the medical studies at the Karolinska Institute are rather unique. From the time of Berzelius, science has played a very important part in their medical curriculum. At the time of Berzelius, even the Royal family went to his lectures. Berzelius and Linnaeus put Sweden on the scientific map and Linneus sent many students abroad to study.

It started very early in Sweden that the medical education included more chemistry and more research than in other countries and the faculty had more research money than any other European faculty of medicine. This was because in about 1915, a wealthy merchant, by the name of Anderson, gave a big grant to the medical faculty for research. On top of it they had already had the Nobel activities that also facilitated the research efforts. That way Sweden was pioneering in research. Sweden was also the first in Europe to have a mandatory general school from 1848.

Bergström started his medical studies at the Karolinska in 1933, and after half a year he was already taking part in research in the medical chemistry department, parallel with his medical studies. He went to America in 1940 and spent a year and a half at Columbia University and at the Squibb Pharmaceutical Company. When he returned to Sweden, he did his dissertation on cholesterol oxidation. Professor von Euler had isolated some

factors, he didn't know what they were, from various tissues that reduced the blood pressure and contracted smooth muscles, and he asked Bergström to look into these factors. That is how Bergström started his work with the prostaglandins in 1947. Then he went to Lund and got a professorship there and stayed there for ten years and spent much of his time on bileacids and steroids along with continuing the prostaglandin research. By 1960, he and his students found that prostaglandins had many physiological activities and they got many clinical colleagues to participate in blood pressure investigations. Instrumentation and innovative application of the physical techniques was a decisive factor in his research. Dr. Ragnar Ryhage was his assistant who combined gas chromatography and mass spectrometry. He also constructed a very popular mass spectrometer that went into production and was in use for a decade.

The most active research area was the fertility field, which became part of a feasibility study of the World Health Organization (WHO). That study resulted in starting a unique research program in WHO by voluntary contributions to what was called a Special Program on Research on Fertility. Bergström was chairman of the prostaglandin area, which included the interruption of pregnancy. They had clinical trials in many countries and especially in developing countries. It turned out that the methyl analog of prostaglandin $F_{2\alpha}$ is the strongest drug known to stop bleeding after delivery. About 600,000 women died annually from bleeding to death after giving birth. The number of occurrences was especially striking in India. To stress the seriousness of this problem, Bergström mentions an airplane crash killing twenty passengers and that the type of airplane involved was grounded for five years. The number of women who died every year from after delivery bleeding corresponded to one full plane crashing every day.

The special program in human reproduction turned out to be very successful. Then Bergström participated in starting a similar program on tropical diseases. That proved to be the most successful program WHO has ever started. Again, all this was done by voluntary contributions by member states and the scientists were in full control of the project. Bergström was chairman of the advisory committee of medical research of WHO at one time. Each of the six regions of the world had one such committee and Bergström as chair of the global committee visited every region every year. When his term was up, he continued his work in India, collaborating there with two companies. One was the partly Swedish Astra and the other was a purely Indian company. They are providing about a million women with prostaglandins upon their delivery. The last chemical work Bergström

did was with 15-methyl prostaglandin $F_2\alpha$, which was in connection with its instability. It had to be kept refrigerated and that is very difficult in the countryside in India. They managed to change the pH of the solution and that made it stable up to 40°C for several years. It is distributed now in a simple little plastic device, containing the solution and a one-time syringe. The point is to get the drug into the woman and then it stops the bleeding, or stops it at least for hours during which she can be transported. It is a formidable task to get these devices out into all the villages in India. It is very inexpensive and the price is established in such a way that the middle class pays partly for subsidizing the device for the poor people.

Bergström finds it a great challenge for a researcher whose work has clinical relevance how to divide his time between research and applications and promotion. The subtitle of his Nobel lecture was "From the Laboratory to the Clinic" to which he would now add, "and to the Village." Eventually he had to leave fundamental research when he became Dean and Rector. He was also a Member of the Board of Directors of the Astra Company in Sweden for ten years.

He has met many interesting scientists throughout his career. Back at Columbia University he met Erwin Chargaff, even before he switched to DNA research. Another interesting man there was Rudolf Schoenheimer, the man who started work with isotopes for studying metabolism. He knew another pioneer, Georg Hevesy, in Stockholm. It was Hevesy who recommended Bergström to become a Member of the Royal Swedish Academy of Sciences.

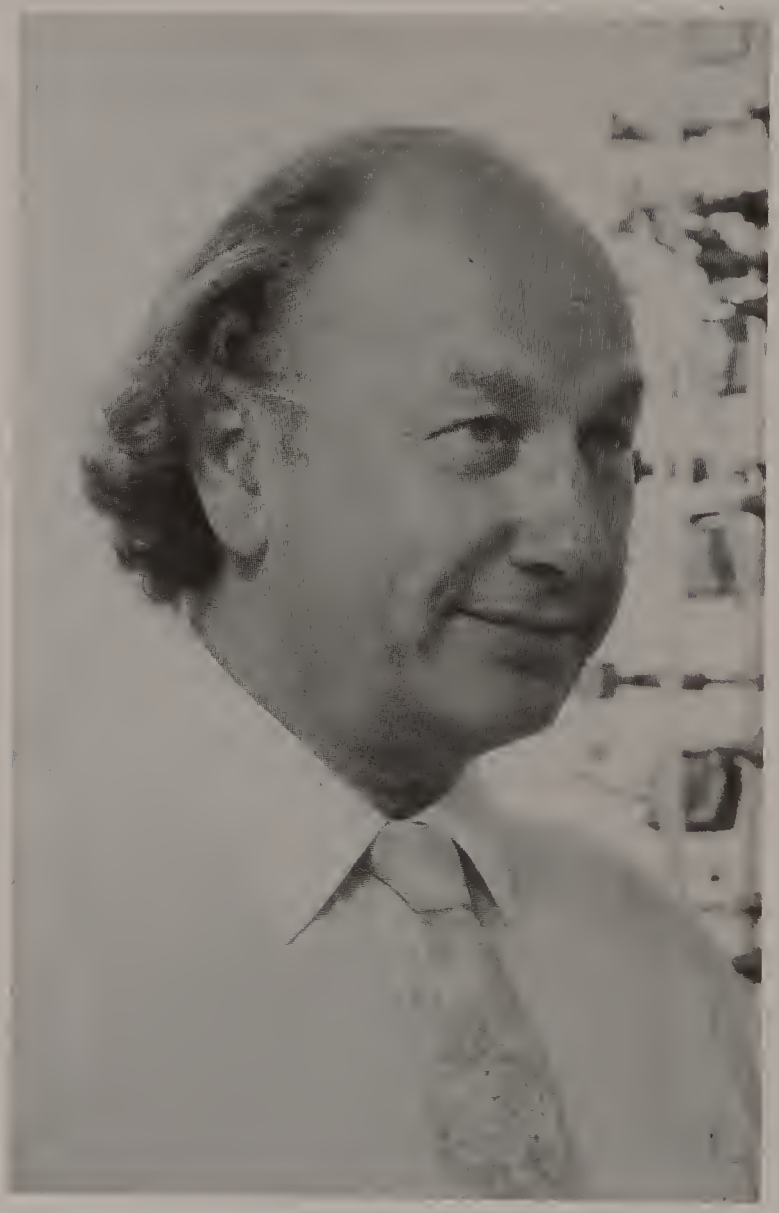
According to Bergström, the Nobel activities are a great stimulant of science in Sweden. One of the reasons of the extraordinary high prestige of the Nobel Prize is that Nobel started it very early and he started it as an international prize from the very beginning. This made an incredible impact at that time. The Swedish King said, "No, no, you cannot give this internationally, it should be for the Swedes." But they managed to resolve the controversy and keep it international.

His own Nobel Prize in 1982 did not change Bergström's life. The only advantage he mentions was that when he was traveling and was trying to get things done in developing countries, his Nobel Prize made it easier for him to see a minister. But, he maintains, in the western world, it did not make any difference, except, maybe, he got more invitations for lectures.

Bergström used to be a very efficient Rector of the Karolinska Institute who often dealt with problems of personnel cutting across all bureaucratic red tape. Someone said that he "had the administration in his pocket,"

to which Bergström responds, "I was certainly non-bureaucratic." He adds that you don't get very far in science without being a little aggressive.

When asked for a message for budding scientists, Professor Bergström stresses the importance of travel, visits to various environments, and to see the world for yourself.



John R. Vane (courtesy of John Vane).

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John R. Vane

John R. Vane (b. 1927 in Tardebigg, Worcestershire, U.K.) is Honorary President of the William Harvey Research Institute, St. Bartholomew's and The Royal London School of Medicine & Dentistry, Queen Mary and Westfield College of the University of London. He shared the 1982 Nobel Prize in Physiology or Medicine with K. Sune D. Bergström and Bengt I. Samuelsson, both of the Karolinska Institute, Stockholm, "for their discoveries concerning prostaglandins and related biologically active substances."

John Vane received his B.Sc. in chemistry from the University of Birmingham (1946), and his B.Sc. in pharmacology (1949) and his D.Phil. (1953) and D.Sc. (1970) all from the University of Oxford. He spent 18 years as a Research Scientist at the Royal College of Surgeons of England, where he was Professor during the last seven years. Between 1973 and 1985, he was Group Research and Development Director at the Wellcome Foundation. He has been at the William Harvey Research Institute, which he founded, since 1986. His name is associated with famous drugs, such as captopril, tracrium, flolan, zovirax, and lamictal.

Dr. Vane was elected Fellow of the Royal Society (London) in 1974 and awarded its Royal Medal in 1989. He was knighted in 1984 for his services to pharmaceutical sciences. Our conversation was recorded in Professor Vane's office at the William Harvey Research Institute on October 12, 1998. At the very beginning of the conversation, Dr. Vane received news of the announcement of the 1998 Nobel Prize in Physiology or Medicine for work on nitric oxide, so

it was an obvious question to ask him about it at the beginning of the interview.*

The area of nitric oxide research, which was cited for the 1998 Nobel Prize in Physiology or Medicine, is one in which you have also worked. Would you care to comment on the 1998 Nobel Prize?

Salvador Moncada was my Ph.D. student and has been a friend and colleague for many years. He has played a leading role in the field of nitric oxide, and I was hugely disappointed that he was not among the winners. For every Nobel Prize, there is a grouping of people who are working their way up the pyramid, getting closer and closer to the pinnacle. As a Nobel laureate, I can nominate for the prize and have been doing so for the nitric oxide field for several years, but my nominees have always included Salvador. One possible difficulty is that Nobel specified that a maximum of three people could share the prize and there were obviously four in the race.

How did your career in science begin?

My interest in science began when my parents gave me a chemistry set for Christmas when I was 12 years old. I began to do experiments in my mother's kitchen, using a Bunsen burner attached to the gas stove. That went quite well for a while until a stink bomb that I had made exploded and caused a color change where it spattered the paintwork, which my father had just redone. He then decided that it would be a good idea to get me out of the kitchen. He owned a small company that built greenhouses and garden sheds. So he built me a garden shed and he had it serviced with water and gas and that became my first laboratory.

I did well in sciences in school. As far as chemistry is concerned, a teacher called Perky Lambert maintained my enthusiasm for chemistry. I went on to specialize in chemistry, physics, and math. I was no good at foreign languages. Then I went to the University of Birmingham, which was across the road from my school, to continue my studies in chemistry.

University chemistry was a big disappointment because the experiments in the practical classes turned out to be just following recipes. This was

*This interview was originally published in *The Chemical Intelligencer* **1999**, *5*(4), 18–25
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organic chemistry and the only excitement was whether you got a 50, 60, 70, or 80 percent yield of the substance you wanted. When my professor, the sugar chemist Maurice Stacey, who died a few years ago, said to me, "Vane, what do you want to do?," I said, "Anything but chemistry." Stacey then said that the Professor of Pharmacology in Oxford was looking for a young man like me. I had to go to the library to look up what the word pharmacology meant.

I went to Professor Harold Burn in Oxford. He was a great enthusiast and a very good teacher. A month after I got there, he called me into his office and said, "Vane: this is not good enough: you must do better." It was a very nonspecific statement. It turned out that he did this to all his students exactly a month after they arrived! He taught me biological methods; he was a great expert in bioassay, using contractions and relaxations of the smooth muscle in bits of animal tissues to detect different substances. He was the father of my career as a scientist, which has been mostly associated with bioassay. Without the ability to assay things on biological tissues, I would have not made the discoveries that I made.

I did a B.Sc. degree with Burn, which is equivalent to an M.Sc. in other universities. Then, following 10 months of research in Sheffield, I managed to go back to Oxford to work with Geoffrey Dawes. He was then Director of the Nuffield Institute for Medical Research, which was housed in the old observatory building known as the "Tower of the Winds," and I took my D.Phil. degree there. Dawes was studying the fetal circulation, using anaesthetized pregnant sheep. At the end of an experiment, I was appointed chief butcher. Meat was still rationed in those days in England, and I used to help to carve up the sheep and distribute it to the hungry Ph.D. students. We checked the regulations, which said that the carcasses should be incinerated, but they did not say by how much!

When I was working for my D.Phil., I acted as demonstrator in Burn's Department in Pharmacology. There, I met Arnold Welch, visiting from America, and he invited me to take a post-doctoral period in the Department of Pharmacology at Yale University, where he had just been appointed Chairman. He was a biochemist, and at that time pharmacology in the United States was dominated by biochemists. He invited me as a "classical" pharmacologist to his department to help to "balance it better." I spent two happy years at Yale with my wife, who was trained as an English and drama teacher, and two daughters, aged two and three and a half years. We made many lasting friends in New Haven and still see many of them.

Ulf von Euler (1905–1983) and Harold Burn during the International Pharmacological Congress in 1978 in Paris. Von Euler discovered the smooth-muscle-contracting activity in semen and named it prostaglandin because he thought it came from the prostate gland. He received the Nobel Prize in Physiology or Medicine for 1970. We now know that most tissues in the body make prostaglandins, of which the ones in semen turned out to be PGE_1, PGE_2, and PGE_{2a}. Harold Burn was the Professor of Pharmacology at Oxford who took John Vane as a student and molded his scientific career (courtesy of John Vane).

In 1955, we came back to England and I joined the Department of Pharmacology of the Royal College of Surgeons, where Bill Paton had just been appointed Professor. We worked independently but there were subjects on which we had a mutual interest, such as the gastrointestinal tract. He was the man who discovered the first antihypertensive drug, called hexamethonium. It was in the College of Surgeons that I invented my first real bioassay tissue. That was using a zigzag strip of the stomach of the rat to assay 5-hydroxytryptamine (5-HT). The long strip contracted in a dose-dependent fashion to 5HT. The rat stomach strip is still being used as an assay tissue, not only for 5-HT but also for other hormones, including prostaglandins.

Soon I invented my second powerful bioassay tool. Normally, bioassay tissues are kept alive by them in an artificial salt solution with oxygen bubbling through in a little organ bath. My reasoning was that if one used this imitation of blood to keep the tissues alive, why not use blood itself? So I pumped a constant small stream of arterial blood from an anaesthetized cat and let it bathe tissues chosen for their selectivity for

different substances. The blood then was returned to the cat. In this way, we were continuously monitoring the arterial blood for changes in the levels of the hormones we were interested in. Then, when we did something to the cat, which, for instance, stimulated the release of adrenaline, within less than a minute, the tissues were relaxing to the circulating adrenaline and the levers which were recording the lengths of the tissues on a kymograph printed out the degree of release before our very eyes. This turned out to be a very powerful technique, which obviated the need to remove individual blood samples, process them, and use chemical methods to obtain the results a few days later. Here was a technique whereby you could see the release or removal of a hormone when it was happening. Looking back on my research life that is the kind of experiment that I enjoy. It is an experiment that you can start in the morning and finish in the evening. Experiments where you have to process samples and wait for days to obtain the answer have never appealed to me. That particular technique led me to make discoveries in many different fields.

The body is an incredibly powerful system. For instance, the kidney releases an enzyme called renin into the bloodstream, where it encounters a protein called angiotensinogen. Renin releases an inactive decapeptide called angiotensin I from the protein. There is also a second enzyme called angiotensin converting enzyme or ACE, which chops two amino acids off the end of angiotensin I and makes it into the most powerful pressor agent that was then known in the body. The dogma at that time was that angiotensin I was converted into angiotensin II by ACE in the bloodstream. What I was able to show, by infusing angiotensin I intravenously, was that the amount of ACE in the blood was too little to be effective, but angiotensin I was converted into angiotensin II in the lungs. The enzyme was in the pulmonary circulation. It took two seconds or so for the blood to go through the lungs and for the conversion to take place. That localized the ACE, which was later found to be in the endothelial cells throughout the circulation. The reason we located ACE in the lungs was that they contain about half of the endothelial cells in the body.

At the same time that we were working on this, I had a postdoc, Sergio Ferreira, coming from Brazil, carrying in his pocket a crude dried extract of venom from a Brazilian snake called *Bothrops jararaca*. He had worked on this venom extract for his Ph.D. thesis and found that it contained a peptide, which potentiated the actions of bradykinin, a powerful vasodilator which was also found in the venom. I asked another colleague of mine,

Mick Bahkle, to test the venom extract on the renin-angiotensin system, and he found that it was a potent inhibitor of ACE. By this time, Arnold Welch had become research director of the drug company Squibb and he asked me to be a consultant. I went to New Jersey three times a year and talked to the management and the pharmacologists. I took with me the idea that here, in this mixture of peptides, which had not yet been characterized, could be the basis of proving whether angiotensin II was a cause of high blood pressure. If it was, then there might also be the makings of a new antihypertensive drug. The scientists were enthusiastic about it. The chemists concentrated on a nonapeptide. At this time, Sergio Ferreira had returned to Brazil, and he and his colleagues were working on another peptide from the venom, which was a pentapeptide. Eventually, Squibb made the nonapeptide in a 1 kilogram sample. However, the marketing people did not support the program at all. They said that nobody could sell an injectable antihypertensive, especially if it was derived from snake venom. In London, with the help of some clinical colleagues, we showed that the nonapeptide (known as teprotide) prevented the conversion of angiotensin I to angiotensin II when injected intravenously into volunteers. John Laragh, who was one of the leading physicians in cardiovascular medicine in New York, then gave it intravenously to some patients with high blood pressure and found that it lowered the blood pressure. So the concept was proved!

In 1973, I was offered the job of Group R&D Director for the Wellcome Foundation and I had to give up my consultancy with Squibb. The Squibb scientists went on to turn this nonapeptide into an orally active medicine, captopril, which is now selling billions of dollars worth around the world. I look on myself as the father of that drug and of the many others like it that have been developed. That story took place in the late 1960s and early 1970s. Interestingly, some years later, Sergio told me that he had wanted to do his postdoc with Bill Paton, who had by then moved to Oxford. However, his wife, Clotilde, was anxious to take a Ph.D. at the London School of Economics, just round the corner from the Royal College of Surgeons, and so he chose my lab to please his wife! Had he chosen Oxford, we may never have had ACE inhibitors!

In 1971, we discovered the mode of action of aspirin. This was also at the Royal College of Surgeons. I was working at the time on anaphylaxis in lung tissue with my Ph.D. student Priscilla Piper. We sensitized guinea pigs to egg albumin and, some 20 days later, isolated the lungs, perfused them with an artificial salt solution, and directed the effluent over two

banks of my bioassay tissues, so that we could record simultaneously from six tissues. When we injected a little egg albumin into the lungs to cause anaphylaxis and we measured the mediators released on our assay tissues, we found histamine, which we knew would be there, and also SRS-A [slow-reacting substance of anaphylaxis]. What was new was that there was a release of prostaglandins, which had not before been implicated in shock. We also discovered an unknown compound, which contracted the rabbit aorta, and we called it rabbit aorta contracting substance, or RCS. These initials had a dual significance since we worked at the Royal College of Surgeons. We also showed that aspirin inhibited the release of RCS. We were so excited by this that we did not notice the effects on prostaglandin release.

It was out of these experiments that, when I was writing a review over the weekend on the actions of prostaglandins, I had the idea that maybe aspirin, in some way, was interfering with the release of prostaglandins. The activities of prostaglandins were all things that aspirin interfered with. This and other experiments led me to the idea that aspirin was interfering with the formation of prostaglandins. To do that, aspirin had to inhibit the enzyme that makes prostaglandins in the body. I went into the lab on Monday morning and called a few colleagues in and I said, "I believe I know how aspirin works. It is working by inhibiting the enzyme that makes prostaglandins, and maybe RCS is a prostaglandin too." I went to the library and found that there had been a paper written by Erik Ånggård and Bengt Samuelsson in Stockholm, describing the preparation of the enzyme, which we then called prostaglandin synthase, from the very tissue we were using, the guinea pig lung.

At this point I made my first ever enzyme preparation. As a pharmacologist, I believed in using whole tissues and not grinding them up. But this time I ground up some guinea pig lungs and spun off the cell debris, leaving the enzyme in the cell-free supernatant. This enzyme in test tubes generated prostaglandins from arachidonic acid. I measured the prostaglandins by bioassay and I found that in a dose-related fashion, indomethacin, aspirin, and salicylic acid all inhibited the biosynthesis of the prostaglandins. This was published in *Nature* along with two other papers. At that time Sergio Ferreira was working with me and Salvador Moncada had just come from Honduras, and they did some work *in vivo*, which resulted in the second paper. At the same time, Smith and Willis, who were Ph.D. students, were working in a different part of the laboratory on the idea that aspirin was interfering with phospholipase A_2. It did not, and they published a third

paper. We had lots of messages from various people who found those papers very interesting. There had been no link between prostaglandins and aspirin before. Over the next few years, we were able to change my hypothesis into a unifying theory in terms of how aspirin and similar substances worked. We showed that all of the aspirin-like drugs then known would inhibit the biosynthesis of prostaglandins. That was a very productive time in our laboratory.

Did you try other substances?

We tried morphine and many other types of drugs, such as antihistamines, anti-malarials, and many others from the textbooks on pharmacology, and they did not interfere with the activity of prostaglandin synthase, which we now call cyclo-oxygenase, or Cox.

Then, in 1973, I became Group R&D Director at the Wellcome Foundation, U.K. I did not quite know what I was getting into. It was like moving from driving a speedboat where you could change direction and cut corners very fast, which was my laboratory at the Royal College of Surgeons of about 30 people, to driving an oil tanker. The R&D Directorate at Wellcome numbered about 3000 people and I was the overall head. If you wanted to change direction and turned the wheel, it took forever for the beast to respond.

I only went there on the promise from the Chairman that I could maintain my own research and have my own prostaglandin laboratory there, which I did. I took Sergio Ferreira with me and later Salvador Moncada joined me also. After receiving his Ph.D., he had tried for a year to do research in Honduras but found that it was impossible.

We had a very productive time at Wellcome. I was fortunate in being able to pick good students, amongst them Sergio Ferreira, Salvador Moncada, Rod Flower, Brendan Whittle, Gerry Higgs, Arnie Herman, and others, who are now in very high positions in pharmacology in the world. Henry Wellcome, when he died, confused everybody. He called his charity the Wellcome Trust and it owned the Wellcome Foundation, which was the pharmaceutical company. I worked for the drug company and we were expected to find new drugs, which I did. During that process, in 1975, we discovered a new prostaglandin. The endothelial linings of blood vessels made it, and its most important properties, which we were able to show before we even knew what it was, were that it prevented platelets from aggregating and caused vasodilatation. The chemists at Wellcome, and we had many chemists there,

had no experience with prostaglandins. They said that it would take them two years to build up a team with experience in prostaglandins. We desperately wanted to know the identity of the substance made by the endothelial cells, which we called PGX. We knew it was a prostaglandin because aspirin inhibited its formation. So we went to the Upjohn Company, which was the world leader in the chemistry of prostaglandins. We at Wellcome had become world leaders in the biology of prostaglandins. I took Salvador Moncada with me. We told them what PGX did, and we suggested collaboration in order to discover the identity of PGX. They went into caucus and, after about half an hour, they said yes. It is very unusual in the drug industry for two rival companies to collaborate together on research, but we did. We sent two scientists to their labs in Kalamazoo. In six months we knew what PGX was. We called it prostacyclin, and that research was a very significant advance in understanding how blood vessels

First Prostaglandin Research group, 1974. In the front: Dr. Janina Staszewska-Barczak (Poland); standing: Dr. John Salmon (U.K.), Prof. Salvador Moncada (Honduras), Prof. Sergio Ferreira (Brazil), Ms. Cheryl Marsh (U.K.), Ms. Millicent Parsons (U.K.), Sir John Vane; back row, standing: Dr. Gerry Higgs (U.K.), Dr. Geoffrey Blackwell (U.K.), Prof. Rod Flower (U.K.). This group was assembled to study the pharmacology of prostaglandins and related substances at the Wellcome Research Laboratories at Beckenham, Kent (courtesy of John Vane).

Sune Bergström, John Vane, and Bengt Samuelsson, about to receive the Nobel Prize from King Gustav in Stockholm, 1982 (courtesy of John Vane).

John Vane with two of his senior colleagues who went with him to Stockholm in 1982 to celebrate the Nobel Prize: Sergio Ferreira (in the middle) and Salvador Moncada (courtesy of John Vane).

keep their inside surface clean. Prostacyclin prevents cells and platelets from sticking to the blood vessels. The aspirin work and prostacyclin were cited for my Nobel Prize in 1982.

Did the Nobel Prize change your life?

Yes, it changed my life in that it opened up new opportunities rather than it becoming an isolating experience. Many invitations to give lectures rolled in and these led to a clearer focus on my work. It gave me opportunities to be more politically orientated, but I did not want that. So I turned down invitations to give lectures on topics about which I knew nothing. There are regular meetings in different countries for Nobel laureates of all disciplines, which I have consistently avoided. I do not want to get involved in the politics of Nobel Prize winners.

In 1984, I was knighted (because of the Nobel Prize), for my services to pharmaceutical sciences. That also was a memorable event; the Queen touches you on the shoulder with a sword. That also changed my life, for in the U.K., being a "Sir" is recognized more than being a Nobel laureate. I was able more easily to book good restaurants or seats in theaters and so on. I said to my wife that we were now in a different orbit and I think she agrees.

In 1984–85, I was still on the Board of the Wellcome Foundation but I was beginning to have problems with the Chairman. He wished the R&D Directorate to go in a different direction from the one I wanted to go and he was Chairman. Just after I had been awarded the Nobel Prize, the Board was meeting in a hotel in Singapore and the manager wanted to have his picture taken with me but the Chairman of the Board wanted to get involved because, as far as the Foundation was concerned, he was more important than I was. In October 1985, I resigned, and for a few months I did not know what to do. I talked to various people including the publisher Robert Maxwell, who invited me to lunch. He said, "John, how can I help you?" I said, looking him straight in the eyes, "I am searching for a millionaire to support the foundation of an institute." "I cannot do that," he said. "What I can do is to give you a hundred thousand pounds to help get you started." He called in his secretary and instructed her. He also offered me a column in his *Daily Mirror*, which I would not have to write, just sign. Then we had lunch, and nothing more ever happened. I found out later that other people had very similar experiences with him.

I continued to look for funding and eventually I had lunch with David Jack, now Sir David Jack. We knew each other well, for he was R&D Director at Glaxo. By then I knew I wanted a research grant for five years to start a new institute of cardiovascular research. I asked him for £500 000 per year and he said, "Done." On May 1, 1986, I came here with a secretary and opened the William Harvey Research Institute. I named it after William Harvey because he discovered the circulation of blood and we were working on the circulation of blood. He had also worked in St. Bartholomew's Hospital for many years as a physician. Within a couple of years, I built up a staff of 15 people. I designed my office myself to accommodate my collection of pestles and mortars, which has grown over the last 40 years.

The startup of biotechnology companies by university professors is spreading. Does this represent competition for you?

Yes, I suppose that there are some competitive elements insofar as funding is concerned. There is a move within the pharmaceutical industry away from the kind of research base that I had developed at Wellcome. At Wellcome there was a tradition, started by George Hitchings and Trudy Elion in the American research labs at Burroughs Wellcome in North Carolina, of developing a research base within the industry and using it to discover new drugs. Nowadays the industry giants are becoming development agencies, depending more and more on small biotech companies or universities to provide the research momentum for them. So we compete with biotech companies for funding from the industry.

I have acted as research adviser for several small biotech companies. One of them is United Therapeutics in the United States, which was started by a remarkable lady, Martine Rothblatt, who recruited scientists who had worked at Burroughs Wellcome on the clinical trials of prostacyclin. Prostacyclin has found its best use in pulmonary hypertension. Intravenous infusion of prostacyclin helps people with primary pulmonary hypertension. Martine Rothblatt has a daughter with pulmonary hypertension, and so she decided to move from the space satellite industry, which she helped to create, into the biotech research industry. She became CEO of United Therapeutics, and the company is now working on prostacyclin and its analogues in order to develop new drugs for pulmonary hypertension and for cardiovascular diseases.

I started a biotech company myself about six years ago. "William Harvey" was going very well, and I had recruited several good friends from various

centers, including the pharmaceutical industry. When I retired as the Director General just over a year ago, we had 9 professorial groups, and about 120 staff, including 30 Ph.D. students. The William Harvey is a research institution supported by charities and by the industry. Its objectives are to find new methods of finding drugs, new biological processes, which would lead to the discovery of drugs, new concepts. We hold some patents. We are linked with Queen Mary and Westfield College of the London University. William Harvey is independent and we have our own charitable status. We also run a very successful conference organization.

Do you use combinatorial chemistry as one of the approaches in looking for new drugs?

One of the mistakes I made when I founded this institute was not to have a chemistry department. All our chemistry is done externally. The kind of hypothesis that is tested in the Institute is, for example, "Are oxidized lipids important in atherosclerosis? Is Vitamin E or Vitamin C important in preventing atherosclerosis?" In my own work we concentrated on the biology of endothelin, which was discovered in 1988. It is a very potent pressor peptide, even stronger than angiotensin II. The Japanese discovered it, and I was fortunate enough to be in Japan the week after the discovery was announced. I brought back a sample and we did a lot of work on it. We also worked on EDRF [endothelium-derived relaxing factor]. We were in that race for several years, but Salvador Moncada beat us and everyone else to the discovery that EDRF was nitric oxide.

Our most recent work derived from my discovery that aspirin-like drugs inhibit the enzyme Cox, which I described earlier. What was puzzling was that even though these drugs had their anti-inflammatory effects through inhibition of prostaglandin biosynthesis, they also shared a general group of side effects. They tended to damage the stomach and the kidney and prolonged the birth process. I suggested that these side effects were due to inhibition of the release of a physiological prostaglandin that was protecting the stomach and the kidneys. Ten years ago, it was discovered that Cox was not just one enzyme, but there were two enzymes, now called Cox-1 and Cox-2, encoded by different genes. Up to then, we did not know why the side effects of anti-inflammatory drugs varied. Ibuprofen, for instance, had less serious side effects on the stomach than piroxicam. Cox-1 is responsible for making prostaglandins, which protect the stomach and the kidneys, while the other one, Cox-2, is induced by inflammatory stimuli and makes

prostaglandins, which contribute to the inflammation. We became interested in Cox-1 and Cox-2 and asked the question "Are the effects of aspirin-like drugs different in their toxicity because they have different effects on Cox-1, which is the enzyme which protects the stomach?" We published a paper in 1994, saying, yes, that is a reason.

Would you care to say something about your family background?

My father was a Russian Jew and my mother was an English farmer's daughter. My father came here as a small boy, a hundred years ago, and I have no idea what his original name was. My father never talked about his background and tried to disguise the fact that he was Jewish. After he died, my mother told me a little about his background. She knew his father and mother briefly. They were from the Russian upper classes. My mother talked about a picture of my grandfather, an oil painting of him, which she had seen. One of my daughters tried to find out what my father's name was before he changed it. She went to Somerset House but they could not help without knowing his original name. My father was a successful small businessman. He died in 1952 before I had a D.Phil. from Oxford. It was a great pity that he did not witness my success but my mother did. She died though before my major prizes.

Is there anything that you would like to add?

I would like to tell you a little about Vanguard Medica. Six years ago, Erik Ånggård and I had a discussion about the pharmaceutical industry, in which we had both worked. Erik and I thought that there must be many compounds on the shelves of industry, which could be very important but their development may have been stopped for reasons, which did not involve toxicology. Perhaps the R&D changed direction or the marketing people did not support them because they were perceived as being unprofitable. So I had a dinner party for six of my R&D director friends, who were all available, and we agreed to start a company whose objective would be to pick up compounds from the giant companies and add value to them and sell them on. It would be a virtual company. We started to look for funding. We went first to Mr. Korda, the nephew of Alexander Korda, who is a venture capitalist, but he just brushed us off. Then we met André Lamott, who is with Medical Science Partners in Boston, and he became our fairy godmother. He gave as a quarter of a million dollars in order to write a business plan. To cut a long story short, we, the seven

of us, as founding directors, wrote to our friends in industry and were offered 200 compounds of the kind we were looking for. We selected four or five to go ahead with. Our lead compound was an antimigraine drug, which Smith, Kline, Beecham (SKB) offered to us. We developed it through phase 3 clinical trials successfully, but then SKB decided not to proceed with the development. By this time we had successfully launched our shares on the London Stock Exchange at £3.10 and they quickly went up to £6.25, but they have now fallen back with the rest of the biotech industry. I am very proud of this company, which now has some 50 employees. The name Vanguard derives from Vane and Ånggård.

Salvador Moncada, 2000 (photograph by I. Hargittai).

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Salvador Moncada

Salvador Moncada (b. 1944 in Tegucigalpa, Honduras) is Director of The Wolfson Institute for Biomedical Research, University College London (UCL), England. He graduated as Doctor of Medicine and Surgery from the School of Medicine, University of El Salvador, San Salvador, in 1970. He then received his Ph.D. degree in pharmacology from the Royal College of Surgeons, University of London, in 1973. The University of London conferred on him the D.Sc. degree in 1983.

Dr. Moncada worked for brief spells in El Salvador and in Honduras in 1969–1971 and in 1974–1975. He worked for the Wellcome Research Laboratories between 1975–1995, serving as Director of Research (U.K.) during the second half of his term. He has been at UCL since 1995. His two main research areas have been prostaglandin and nitric oxide. He is most famous for having identified the so-called endothelium-derived relaxing factor (EDRF) as nitric oxide. In the 1990s, with over 30 thousand citations he was one of the most cited scientists in the world and the most cited British scientist by a large margin. When the 1998 Nobel Prize in Physiology or Medicine was announced and Moncada was not among the three awardees, an international uproar followed with people calling it, among other things, injustice and suggesting that the Nobel Committee was re-writing science history.

Dr. Moncada was elected Fellow of the Royal Society (London) in 1988 and he is a Member of the Academia Europaea (1992), Foreign Member of the National Academy of Sciences of the United States, among many other memberships of learned societies. His numerous awards include the Royal Medal of the Royal Society (1994).

We recorded our conversation in Professor Moncada's office in London on February 10, 2000.

You were expected by many to win the Nobel Prize for nitric oxide (NO) research but you were not among those awarded in 1998. Would you care to tell me what do you think happened?

I don't know. And it is impossible to know since no records are ever published on the reasons why a decision is made. So it is useless to speculate. I think that institutions can give prizes to whoever they want, that is their prerogative. The problem with the Nobel is that it has become so preeminent that it tends, when mistakes are made, to "rewrite history."

I have said before that I am extremely proud of our contribution to the birth and development of this field. Our work on the identification of NO was the earliest and has been recognized as such by the scientific community at large. The techniques we developed for this are now universally used. We identified the biochemical pathway to the synthesis of NO and made many more seminal contributions.

Now, when a scientific discovery is made it illuminates not only lines for future research but also the past and things, which were scattered in the literature, suddenly come together. That, however, is hindsight!

Let me give you an example. In the 1970s, a Japanese group led by Deguchi, found that L-arginine stimulated the enzyme, soluble guanylate cyclase. This is probably the closest work to the discovery of the L-arginine: NO pathway, which is the discovery we are talking about. Those workers, however, were not aware of the great significance of their work. This only became apparent some 10 years later. However, if we are to recognize the prehistory of this discovery, these workers have as much claim as anybody else. The history of science is full of incidents, which precede a discovery and can be connected with it only after the discovery takes place.

Having said that, I know of no case in which such a significant group of the scientific community has protested so vehemently about the unjust exclusion of a scientist. This is reassuring. I am very happy about the recognition, which I have received through peer review, the most objective form of recognition. On the 1998 decision about the physiology and medicine prize, the Nobel Committee was very much at odds with the scientific community.

I would like to ask you about your background, education and career.

I come from a mixed background. I was born in Honduras but my mother came from Central Europe. She was born in a small town in northwest Romania. Her name was Jenny Seidner and she was of German Jewish stock. My maternal grandfather was an Austrian Jew who fought in the World War I. My mother died some years ago. My father on the other hand, is a Central American of Spanish descent, most probably Catalan, since my surname, Moncada, comes from that region. So I grew up in a mixed Catholic and Jewish household but since my father was not a strong Catholic, the Jewish religion predominated. I went many more times to the synagogue than to the church until the age of 13 when I decided not to do the Bar Mitzvah. At that point, I abandoned religion for many years, until, about 12 years ago when, being by chance in Amsterdam on the date of the Jewish New Year, I decided to visit the old synagogue out of curiosity. The service was very moving. It touched me deeply, more so when I realized that a number of people attending had Spanish or Portuguese surnames. These were obviously from old Sephardic families coming from the Iberian Peninsula since the 16th century! I did not become religious suddenly, however it highlighted for me my cultural heritage. I enjoy very much, when I go to the United States, to visit my sister in New York and dine with her and her family for Sabbath. I feel at home. I don't pray but, somehow, I feel extremely comfortable in that environment.

For a variety of circumstances, which would take too long to tell, my grandfather and his family, who left Europe in 1937, did not go to the U.S.A. or Argentina or any of the other places that Jews were emigrating to. Instead they ended up in Honduras! I was born there but my family moved to El Salvador when I was about 4 years old. I grew up in El Salvador and did all my studies to obtain a medical degree in 1970. Fortunately, the Medical School in El Salvador was, at that time, very good. A group of highly talented academics with financial help from the Kellogg and Rockefeller Foundations had modernized medical education in El Salvador so I was exposed to high quality training. However, because of heavy involvement in student politics during my medical studies, I was persecuted and finally expelled from El Salvador shortly after I finished my medical education and ended up back in Honduras. From there, I decided to look for a place for postgraduate training.

Salvador Moncada among his fellow high school students (in the center) at the age 17 in El Salvador (courtesy of Salvador Moncada).

How did you end up in England?

The way I came to England is also an interesting story. I was in Honduras but my wife at the time, who was Salvadorean, was not allowed to join me. I don't know if you are aware of the fact but in 1969, there was a war between El Salvador and Honduras, which was known as the "Football War." That closed communication between the two countries and for us, in 1970, made things extremely difficult. So we were separated for months but used to meet in the neighbouring country of Guatemala.

During one of those trips, we had dinner with a Guatemalan Professor of Physiology whom I knew. I explained to him my problem and said that, although the majority of my classmates were looking for places in the U.S.A. to go for postgraduate training, I was more interested in Europe. He said that he had been in London some 7 or 8 years earlier at the Royal College of Surgeons and that during his stay he had befriended a scientist of about his age, whose name was John Vane. He had not had contact with him for several years but he felt close enough to write to him to see whether he could help. The following morning, after I had

been to the library to see what John Vane was working on, my friend Fernando Molina wrote John a letter of recommendation.

To my great surprise, almost by return of post, I received in Honduras a letter from John saying basically that he did not know who I was, however, if his good friend Molina, recommended me, I was probably all right. Provided I had financing and two other letters of recommendation I could join him in London. That was immensely generous!

I arrived in February 1971 and was extremely lucky from the very beginning. John Vane was starting to work on the hypothesis that aspirin-like drugs might inhibit prostaglandin biosynthesis.

Although my English was almost non-existent, John said that I did not need to take any classes since I would learn in the lab. He sent me there straightaway, guided by a technician who taught me to do bioassay. John said: "Once you learn the technique, add arachidonic acid over the tissues and whatever responses you get, then give aspirin to see if you change them."

It took about a week to show that aspirin was indeed blocking arachidonic acid-induced responses. There was a lot of excitement in the lab because John's own experiments were clearly showing that in lung homogenates aspirin-like drugs were blocking prostaglandin synthesis. Along the corridor, Smith and Willis were also showing in humans that ingestion of aspirin blocked the production of prostaglandins by platelets. At that point, John asked me to join him and Sergio Ferreira in a series of experiments using dog spleens where we showed that aspirin and indomethacin inhibited prostaglandin release from that organ. So within a few months from coming to England, I had my name in one of the three papers, now classics, which describe the mechanism of action of aspirin-like drugs.

What happened next?

I spent the next three years working for my Ph.D., mainly in collaboration with Sergio Ferreira. I think we made several important contributions to the understanding of how prostaglandins participate in the process of inflammation and pain. We developed the concept that prostaglandins are not mediators of inflammation but are instead modulators that act as an amplifying system for inflammatory mediators such as bradykinin and histamine. The concept is now widely accepted.

However, I wanted to go back to Central America. I had the romantic view that I would be able to develop biomedical research in Honduras and, of course, to go back to politics! Shortly after John Vane and a small

group of people moved to Wellcome, I left for Honduras. Soon after that Sergio Ferreira went back to Brazil, thus leaving open the position of head of John Vane's group. John said to me that he would leave that position open for a year in case I decided to come back. I managed to do some research in Honduras but it was immensely difficult and also I again became entangled in politics, so, after about 10 months there, I phoned John and said I was returning.

On my way back, in 1975, I stopped in Florence for the International Meeting of Prostaglandins, where Bengt Samuelsson announced the chemical structure of a substance, the biological activity of which had been identified by John Vane some years earlier. This had been known as rabbit aorta contracting substance, which Bengt renamed thromboxane A_2 and showed it to be generated from platelets.

After the meeting, I came to Wellcome where I teamed up with Phil Needleman and Stuart Bunting. Within a few weeks, we isolated and partially characterized the enzyme "thromboxane synthase," a piece of work that we published in *Nature* together with Bengt Samuelsson and Mats Hamberg. Phil Needleman left shortly after the work was finished and we remained interested in thromboxane A_2 and its generating enzyme, for which we had also discovered the first known inhibitor.

Salvador Moncada in the Wellcome Research Laboratory in 1975 (courtesy of Salvador Moncada).

How did you then start working on the vessel wall?

Well, John Vane was interested in mapping the distribution of thromboxane synthase in the body. We had, with Stuart Bunting, developed all the methodology to do that. I however was interested in cutaneous bleeding time and the way in which the hemostatic plug is formed. I had the idea that the vessel wall might be making thromboxane A_2 to synergize with that of the platelets to aggregate them and prevent bleeding. Moreover I had read a paper, which suggested that platelets and the vessel wall share some common proteins and enzymes. So, when Richard Gryglewski joined us shortly after for a sabbatical, I suggested that we should map the distribution of the thomboxane synthase in the body with special emphasis in the vessel wall. We found thromboxane synthase in several tissues, however the golden nugget was indeed in the vessel wall!

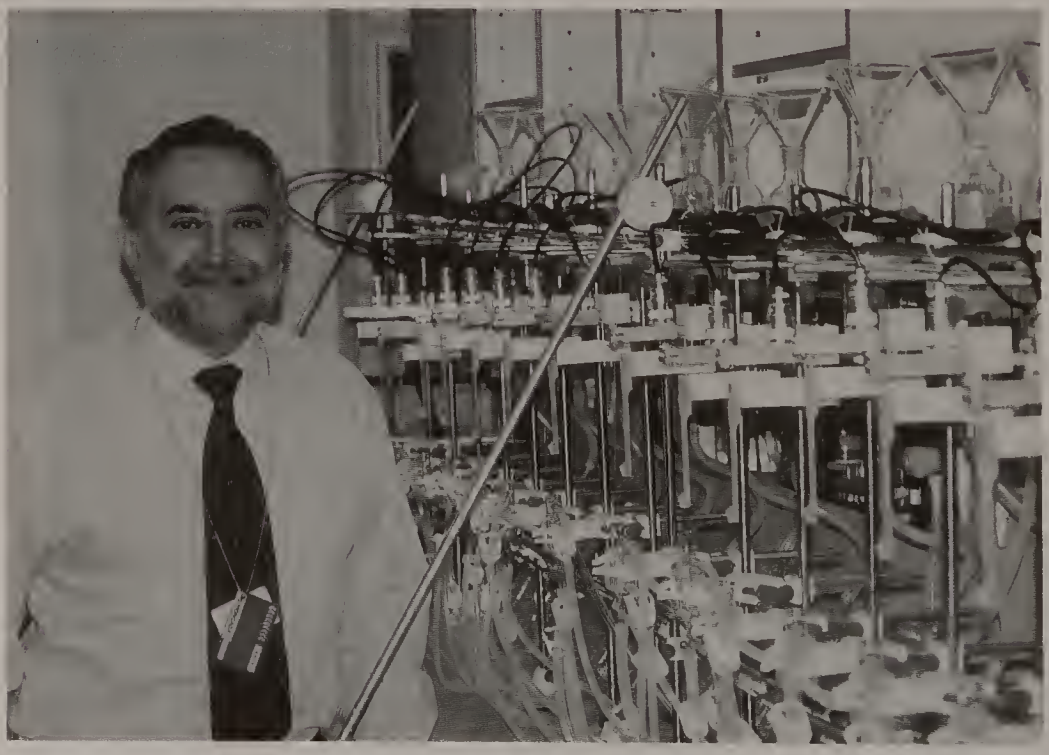
Experiments with a fraction obtained from pig arteries revealed the existence of an enzyme, which was consuming the biochemical substrate that we were using and transforming it not into thromboxane but into a compound that we did not recognize. The new compound, was a chemically unstable vasodilator that we started calling prostaglandin X (PGX).

Probably the most exciting moment in the subsequent weeks came when I followed my hunch that PGX might be an inhibitor of platelet aggregation and, with Stuart Bunting, carried out the experiment, which demonstrated this powerful action. That, I believe, was the most fulfilling moment of insight, which I had during those years. The chemical identification of the compound was achieved by a team of chemists of the Upjohn Company, and biologists from our group. This took place following a confidential disclosure agreement in which I presented the work to scientists of the Upjohn Company. John Vane and I announced the structure of PGX at a conference in Santa Monica, California, on the 3rd of December 1976. I remember the date because it was my thirty-second birthday.

How long did you stay with Wellcome?

For 20 years, from 1975 to 1995 when the merger between Glaxo and Wellcome took place. When John Vane left to set up the William Harvey Institute in 1984, I became Research Director of Wellcome until my departure. Those years included the period when we started to work on endothelium-derived relaxing factor (EDRF), which we later identified as NO.

Salvador Moncada with his daughter Claudia in Madrid, Spain on the occasion of receiving his Doctor honoris causa in 1986 (courtesy of Salvador Moncada).



Salvador Moncada in the laboratory, 2000 (photograph by I. Hargittai).

How would you characterize your relationship with John Vane?

John was my mentor, without him perhaps my scientific career would never have happened. He was a great teacher and we did many good things together.

When did you become independent in your research?

That's difficult to say; however, I feel that by 1975, my research was fully independent. From then on, John and I collaborated closely and had very good synergism.

What was your most important finding on nitric oxide?

We were the first group to provide definitive evidence for the release of NO from vascular endothelial cells and to define the biochemical pathway to its synthesis. Both the methodology we developed and the name that we gave to the pathway (L-arginine: NO) are now universally accepted. We also made several other fundamental contributions to the field.

How did you come to University College London?

At the time of the merger between Glaxo and Wellcome, I was looking for a place where I could recapture and develop the atmosphere that existed in Wellcome. As you know, Wellcome was a unique company, which combined, over the years, a first class scientific base where many fundamental discoveries were made with a flair for drug discovery. I thought that something as special could, in the future, only be reproduced in an enlightened academic environment. I was lucky that such a place existed at University College London.

I had heard that UCL was in the process of buying the Cruciform Building right in the middle of its campus in Central London, and I thought that such a building was ideal for what I wanted to do. I contacted John Pattison, then Dean of the Medical School, and discussed the idea. He became interested and put me in contact with the Provost, Derek Roberts with whom I found I shared many concepts. He is a special man who came to academia from industry. He is a man of vision and outstanding determination. We had several discussions after which he decided that he liked the idea of a coherent Institute in the building that I would direct.

The Cruciform Building of fourfold symmetrical shape next to the center of London University (Newbery Smith Photography Ltd., London — 0208–8679 1689, courtesy of Salvador Moncada).

How could this happen?

I guess we both liked the concept of an academic institute that could lie at the interface between academic endeavor and practical application. Also, although I had been in industry most of my life, I had been very successful in the pursuit of basic science.

I strongly believe that the type of institute that I am now setting up will be a normal feature of university structure in the future. I do not believe that all university research should be carried out with an eye on future practical developments but universities have to be more aware of the practical applications of the knowledge they generate. If nothing else, this will enable them to create alternative sources of funding and cover the present gap in financing from government sources.

But there is more to it. I believe that the difference between basic and applied research is disappearing. During the present scientific revolutions science and technology are often one and the same thing.

Has your dream of an Institute come true?

The Wolfson Institute? Well, it was a dream to convert this marvelous old building into a functional unit. Not many people besides Derek Roberts and John Pattison believed that that could be done! We have restored the building and created well-equipped modern laboratory space. We now need to develop it into a functional unit. We are achieving this through the recruitment of high quality scientific groups.

What is your style of leadership?

None. The best way to run an institute is not to try to run it. Scientists do not want that. They want an open environment, which allows their research to mature and is relaxed and happy. I don't like vertical organizational structures. I prefer flat structures in which people with multiple and exchangeable expertise and interests interact freely. I put a lot of emphasis on human, or better, humane interactions.

Who supports your work?

In the Institute, roughly 50 percent of our support comes from industry and 50 percent from the traditional bodies, which fund academic research, namely the Wellcome Trust, Medical Research Council and BBSRC. As far as my own research is concerned, some money comes from the Wellcome Trust, some from the MRC but the majority originates from a research agreement that I have with Glaxo Wellcome.

What is your present interest in research?

I am interested in the control of cell respiration. The terminal enzyme in the respiratory chain (cytochrome c oxidase or complex IV) is finely controlled by NO. We have recently shown that in vascular endothelium cells, endogenous NO regulates respiration. This has led us to suggest that the oxygen : NO ratio acts in cells as an oxygen sensor determining the amount of oxygen, which is utilized. There is a beauty in that mechanism since NO and oxygen compete with the enzyme. However, I suspect that in that interaction also lie the early changes leading to cell pathology. We already have some evidence for that.

You have made some of the most fundamental contributions to two fields of research, which led to Nobel Prizes. Do you think there might be a third one in you?

I love doing research. As far as discovery is concerned, you don't search ... you stumble upon it! You need, however, a mind, which is ready to see the breakthrough when your experimental data don't fit the hypothesis. I guess you have to have an eye for the unusual and I think I have that. As far as prizes are concerned, well, that is another matter ...

What about your personal life?

I have been very lucky. A few years ago I met a woman with whom I have a deep and meaningful relationship. We married two years ago and have been blessed with a little daughter who I adore, she is now eighteen months old. I also have a grown up daughter from my previous marriage. She is a physician, very bright and hard working and I am extremely proud of her.

Do you have heroes?

I always loved non-conformist rebels. My heroes were, in my youth, more political than scientific, namely Gandhi and Bertrand Russell. I admired one for his defiance and success in the face of apparently invincible forces, the second for his tongue-in-cheek criticism of the established social, religious and moral structures of his time. I think that my choice of heroes was dictated by my experience of the immense injustice that existed in the society in which I grew up. In science, I admire Einstein, of course. I like his unusual approach and completely share his view that in science, imagination is more important than knowledge.

Do you think your background matters in your activities?

It is a long way from Central America and I am not talking about physical distances. However, I feel very comfortable here. I have lived in London almost 30 years and England has been good to me.

Are you part of the Establishment?

That would be difficult for a Latin American Jew who didn't go to the right schools or universities, comes from an almost unknown country, does many things in a very different way to that prescribed and speaks English with the wrong accent! Having said that, I have been elected a Fellow of the Royal Society, which is a great honor, and a Foreign Member of the American Academy of Sciences. This latter was for the identification

of NO as a biological mediator and the elucidation of its biochemical pathway.

Did your negative experience, not with science but with the scientific establishment, turn you off?

There is no connection between the two and I don't think I had a bad experience with the scientific establishment. It was the Nobel Committee who put itself in an uncomfortable position in front of the scientific community. My work stands there to be judged by my peers and by the younger scientists that will follow our generation. They have already been immensely supportive and extremely generous in their praise. As far as doing science is concerned, the last 29 years I can exchange for two brief but magnificent moments. The afternoon when I did the experiments that showed the platelet anti-aggregating effect of prostaglandin X and the day Richard Palmer came back to me with the first chemiluminescence tracing showing vascular endothelial cells made NO. I still can recall the excitement and would be immensely happy if I had one such opportunity again.

Robert F. Furchgott, 2000 (photograph by I. Hargittai).

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Robert F. Furchgott

Robert F. Furchgott (b. 1916 in Charleston, South Carolina) is Distinguished Professor at the State University of New York, Health Science Center at Brooklyn and Adjunct Professor at the Department of Pharmacology of the University of Miami School of Medicine. He shared the Nobel Prize in Physiology or Medicine in 1998 with Louis J. Ignarro (b. 1941, UCLA School of Medicine, Los Angeles) and Ferid Murad (b. 1936, University of Texas at Houston) "for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system." Robert Furchgott received his B.Sc. degree in chemistry from the University of North Carolina in 1937 and his Ph.D. in Biochemistry from Northwestern University in 1940. He has been with the Department of Pharmacology of the State University of New York since 1956. His recognitions and awards include the CIBA Award for Hypertension Research (1988) and the Albert Lasker Basic Medical Research Award (1996). We recorded our conversation on May 19, 2000 at the Health Science Center in Brooklyn. First I asked Professor Furchgott about his initial discovery.

I worked with isolated vascular preparations for many years. In the early 1950s, I began using a helically cut strip of rabbit aorta (attached to an isometric recording lever), which allowed quantitative studies of the responses of vascular smooth muscle to various agents. It was an ideal preparation at that time for studying agonists and antagonists and trying to differentiate and characterize the receptors on which they acted. We worked with that preparation for many years. In our first full paper in 1953, we reported

Robert Furchgott in his laboratory at Washington University in St. Louis in 1953 with his first graduate student, Marilyn Wales McCamen. Note the rotating kymograph for recording, with an ink-writing lever, the changes in length of an aortic strip in an organ chamber in a constant-temperature bath. The blind on the window is closed to shield the strip from bright sky-light, since Furchgott had accidentally discovered in the previous year that aortic strips undergo reversible "photorelaxation" when exposed to near ultraviolet light (courtesy of Robert Furchgott).

Robert Furchgott in his laboratory at the State University of New York Downstate Medical Center at Brooklyn in 1970. Aortic strips, mounted in organ chambers, were now connected to isometric force-transducers for continuous recording of changes in tension (courtesy of Robert Furchgott).

results with a number of different agonists, which elicited contractions (like adrenaline, noradrenaline, and histamine) or relaxation (like isoprenaline); and began quantitative studies with some of the antagonists for the receptors on which these agonists act. One of the drugs that we tested was the neurotransmitter acetylcholine. It only produced contraction of the aortic strips. This was surprising because it was well known that acetylcholine when injected intravenously was one of the most potent vasodilating agents known. So it was something of a paradox that with this vascular preparation acetylcholine elicited contraction rather than relaxation. In fact, for many years we used acetylcholine to produce standard levels of contraction of aortic strips on which to compare the potencies of different catecholamines for producing relaxation by their action on β-adrenergic receptors after irreversibly blocking α-adrenergic receptors by pretreatment with dibenamine.

Our general purpose was the differentiation and characterization of receptors. This was before the use of radioligands and, of course, before the advent of molecular biology. The idea was to characterize each type of receptor on the basis of relative potencies of agonists acting on that type of receptor and the dissociation constants of certain antagonists that block the action of the agonists on the receptor. We used a theory based on drug-receptor interaction that was being developed in my lab. Some of the questions had to do with how different agonists, acting on the same receptor, could produce different degrees of contraction when occupying the same fraction of that receptor population.

As already mentioned, we used acetylcholine to produce contractions (after blocking α-adrenergic receptors) on which to determine the relative potencies of different catecholamines acting on β-adrenergic receptors. There was a surprise many years later, in 1978, when we repeated some early experiments on characterizing the adrenergic β-receptors. My technician came in and said something like, "Dr. Furchgott, you said that the acetylcholine (actually it was carbamoylcholine with the generic name of carbachol) would give contractions on which we could study relaxation. I've added it to this preparation and it produced relaxation instead of contraction." This surprised me right away because he was not supposed to add it on a contracted preparation. I thought that my technician had made a mistake, that he had contaminated the acetylcholine. He was not supposed to have added it during a noradrenaline-induced contraction; rather, he was to wash out the noradrenaline and then try the acetylcholin for contraction. Then he was to put in an agent to block the α-adrenergic receptors so that they would be out of the way, and then add acetylcholine

to produce contractions on which to compare the relative potencies of the catecholamines as relaxing agents. But he was right that he hadn't contaminated anything.

Did he skip a step in the experiment?

He forgot to wash out the noradrenaline, which was producing contraction via α-adrenergic receptors, before testing the acetylcholin for its inherent contracting activity. When he added the acetylcholin on two of these preparations, there was a relaxation whereas in the past we'd never seen that. If he had not forgotten to wash out the noradrenaline, we wouldn't have seen the relaxation. That was an accidental discovery.

The question was why do we find now relaxation with acetylcholin whereas in past experiments we observed only contraction. One difference I recognized right away in our procedure was that now we were using transverse rings of rabbit aorta rather than helical strips. We had begun using transverse rings a while back for some technical reasons. It took us about a month or two to understand why there was a difference in response. We found that the lack of relaxing response to acetylcholine in helical strips was the result of unintentional mechanical removal of the endothelial cells in the process of handling the preparations.

We had no idea at first that something was coming out of the endothelial cells. Then we began to speculate that that might be the case and a very simple experiment provided the evidence. Our so-called "sandwich" experiment provided direct evidence. A transverse strip of rabbit aorta freed of endothelial cells and unable to relax on exposure to acetylcholin could be made to relax if it were remounted with its endothelium-free intimal surface placed against the endothelium-containing intimal surface of a longitudinal strip of aorta. So there was a diffusible relaxing factor released from the endothelium.

We thought about various factors. One possibility was a prostaglandin, such as prostacyclin, but that was not the case and we understood that we were dealing with something new. We also found that the response, the endothelium-dependent relaxation, could be produced not only by acetylcholine and related muscarinic agonists, but by a number of other agents. One of them was substance P, which is a polypeptide. We studied the removal of the endothelium both with microscopy with staining and, also, we had friends do electron microscopy for us. It became obvious that you needed the endothelium in order to get relaxation with acetylcholine,

substance P, and some other agents, including ATP, ADP and the calcium ionophore A23187. This last agent provided the first evidence that calcium was playing a role in the release of the relaxing factor. Later on, it came out, not from our work but from work of others, that the enzyme nitric oxide synthase synthesizes the nitric oxide, which is the factor. The nitric oxide synthase in endothelial cells is now called eNOS. It requires a calcium-calmodulin interaction with it in order to be activated to produce nitric oxide by oxidation of a guanidinium nitrogen of L-arginine.

Did you determine the presence of nitric oxide synthase?

We couldn't say at that time whether we were releasing something that was already present or whether we were stimulating an enzyme to make the substance and then release it. It later turned out that the latter was the case. In the meantime a lot of other laboratories got into the act of trying to identify the endothelium-derived relaxing factor (EDRF). It is embarrassing that it took us so long to identify it was NO.

How long did it take?

It took us from 1980 when we first published in *Nature* until 1986. Everybody knew about things like nitroglycerin and nitroprusside giving good relaxation. Ferid Murad had done some of the early work on the effect of the so-called nitrovasodilators stimulating guanylyl cyclase to give cyclic GMP [guanosine monophosphate]. He had found out at an early stage that nitric oxide as a gas would stimulate guanylyl cyclase and give you cyclic GMP and in certain cases relaxation of smooth muscle. One reason Murad's work was so important was that he recognized that nitric oxide would stimulate soluble guanylyl cyclase to form cyclic GMP from GTP [guanosine triphosphate]. In view of the fact that NO by itself did that in his cell-free system, he proposed that all of the nitrovasodilators, like nitroglycerin, nitroprusside, and even sodium nitrite, when added to the system, would stimulate the enzyme by liberating nitric oxide.

Was his work running parallel to yours?

A little bit. He was into the guanylyl cyclase business before we came accidentally across this relaxation of blood vessels by acetylcholin acting through the endothelium to produce EDRF. Ignarro's group was the first to show that nitric oxide itself would give you an increased cyclic GMP

and a relaxation of vascular smooth muscle. I was aware of the work of all these people. In fact, I visited Murad in early 1980 at the University of Virginia and discussed my work and his work and I actually put in one of my 1980 papers that EDRF might well act by stimulating guanylyl cyclase. At first we were going to do some collaborative work but he moved on to Stanford and took on a postdoctoral fellow, Robert Rapaport. They together published what I consider to be the first definitive full paper showing that EDRF stimulates guanylyl cyclase and that, in turn, precedes the relaxation of the muscle.

But he didn't make the connection with NO.

Nobody made it at that time. All of us were aware of the early work with nitric oxide. Ignarro had been involved in it. I knew of his work, I knew of Murad's work but nobody suspected that nitric oxide was a substance that was indigenous to the biological system.

In hindsight, if somebody had walked into your office prior to 1986 and had told you that it should be NO, what would've been your reaction?

It's a bit embarrassing. I had worked previously with nitric oxide, although we didn't make our solutions from the gas directly. I'd had an accidental discovery in my lab back in the 1960s when I assigned a new postdoctoral fellow to obtain a cumulative dose-response curve for sodium nitrite as a relaxing agent on aortic trips contracted with noradrenaline. Having run such an experiment many times, I told him what results could be expected. However, after his experiment, he came in and said, "Dr. Furchgott, I got something very different from what you told me. The sodium nitrite is much more potent than you think." It turned out that in making up dilutions of the nitrite for use in his experiment, he had accidentally used an acidified diluting fluid (0.01 N HCl) from the laboratory shelf (to be used for noradrenaline solutions) rather than the neutral saline diluting fluid next to it. It turned out that this use of acidified sodium nitrite solutions produced HNO_2 (pK_a, 3.2), which immediately and reversibly dimutates to give low concentrations of NO, NO_2 and H_2O. We obtained evidence that the strong but transient relaxations that the postdoctoral fellow had obtained with acidified nitrite were due to the NO in the solution. I put the finding aside. That was before the endothelium story. I then went back to the finding in early 1986.

I had a very good postdoctoral fellow working with me, by the name of Billy Martin from Glasgow, he is now full professor. Martin had tried to extract a neurotransmitter that was responsible for relaxation of certain types of smooth muscle when their nerve was stimulated. This nerve was called NANC nerve, meaning nonadrenergic and noncholinergic. You could block the receptors for adrenaline and noradrenaline, and the muscarinic receptors for acetylcholine and you would still get relaxation of the muscle in response to NANC nerve stimulation. A lot of work on this was being done in John Gillespie's laboratory in Glasgow. He was Head of Pharmacology and Martin was one of his Ph.D. students before he came to work with me.

Martin had attempted to extract the neurotransmitter from the bovine retractor penis muscle, a large smooth muscle with a lot of tissue to work with. He made extracts, which didn't give much relaxation of smooth muscle preparations at all until they were acidified. That reminded me of what we'd observed before. So I decided to test $NaNO_2$ solutions adjusted to different pH levels for relaxation of the rabbit aortic strip. The relaxation as a function of pH was the same as Martin had found for extracts of the bovine retractor penis muscle. Thus, I began to think that maybe nitric oxide is involved in EDRF. Just about that time, early in 1986, two groups had come out with findings that showed that superoxide anion, O_2^-, is a great scavanger of EDRF. One group was under Moncada in England and the other was Rubanyi and Vanhoutte, then at the Mayo Clinic. Their experiments were perfusion bioassays in which EDRF is released from endothelial cells upstream and produces relaxation of endothelium-free rings or strips downstream. Both groups observed a very fast decay of EDRF, but could markedly prolong the decay time by putting in superoxide dismutase. They came up with the idea that superoxide rapidly inactivates EDRF. I began to think that EDRF may be NO, and that superoxide rapidly inactivates it. They are both free radicals. Our work with acidified nitrite and the work that came out about the same time showing that superoxide was a marked scavanger of EDRF led me think that EDRF may be nitric oxide.

When was this?

This was in April 1986. I was making some notes while flying back from a meeting in St. Louis. I also made a note that we should go ahead and see whether nitric oxide and EDRF have similar characteristics? And they did, every way we could compare them.

It must have been a very exciting moment.

It was. I got quite excited about it but I kept it rather secret because a lot of people were working in the field and I didn't want my ideas to come out yet. Actually I came back from this meeting in April and with two assistants Dr. D. Juthianandan and Dr. M. T. Khan we began an intense study on nitric oxide as derived from sodium nitrite under acid conditions. We didn't have a cylinder of nitric oxide in the laboratory at the time. We used acidified nitrite in the early work we reported in June or July 1986 at a meeting at the Mayo Clinic. There I proposed that EDRF is nitric oxide. The title of my report was "Studies on Relaxation of Rabbit Aorta by Sodium Nitrite: The Basis for the Proposal that the Acid Activatable Inhibitory Factor from Bovine Retractor Penis is Inorganic Nitrite and the Endothelium-Derived Relaxing Factor is Nitric Oxide." Unfortunately, it didn't get printed until 1988 [R. F. Furchgott, in *Vasodilation: Vascular Smooth Muscle, Peptides, Autonomic Nerves, and Endothelium.* Ed. P. M. Vanhoutte, Raven Press, New York, 1988, pp. 401–414]. It was a longish title and emphasized more the retractor penis factor than EDRF but at the end it says something about EDRF.

Was it the first time it was suggested that EDRF was NO?

It was the first time in public that it was suggested. Following me on the program at the same meeting was Lou Ignarro and he came up with the same idea, independently from us. He was also impressed by the similarities in the characteristics of nitric oxide and EDRF, on guanylyl cyclase, on inhibition by hemoglobin, by superoxide, and so on.

When you were coming back from St. Louis earlier in 1986, and you asked your assistants to do the tests, did you tell them to keep quiet about it?

Not completely, no.

I would be curious about what was the atmosphere like in your lab in those days?

Quite exciting. We really worked very hard to get all the material together by the time of this international meeting at Mayo Clinic. Dr. Khan and I used perfused segments of rabbit aorta as a source of EDRF in perfusion bioassay experiments and found that EDRF had similar rates of decay as infused NO. Also, EDRF and NO behaved similarly in the presence of

various agents. At the same time Dr. Ignarro and Dr. Moncada were working on the same ideas with perfusion bioassay systems. Moncada was working with R. M. J. Palmer and others in his laboratory at the Wellcome Company and had a very good preparation to work with. He didn't depend on perfusing a large conduit artery the way Ignarro and I did. His perfusion-bioassay had cultured endothelial cells on microbeads. There was a column with beads covered with the cultured cells and through that column he could pass the agents to release EDRF, and he was able to show that the material released from this type of cultured cell was similar to NO. Using that system, by 1987, he was showing that the amount of nitric oxide released from the cultured cells was sufficient to fully account for the relaxation of the endothelium-free strips used to bioassay EDRF downstream. He could match relaxation by EDRF with that of known amounts of infused NO. He measured nitric oxide in the perfusion fluid flowing down from the cultured cells. By the time it came down, a good part of it was already oxidized to nitrite. He would therefore convert any nitrite back to nitric oxide through reduction by iodide in an acid solution and pass the total NO through a nitric oxide gas analyzer which they had developed.

Was this considered to be direct evidence that EDRF was nitric oxide?

This was more direct evidence than the other procedures, such as I had used and Ignarro to some extent. We were saying that EDRF is nitric oxide because the characteristics, decay and behavior to blocking agents, and so on, were all similar. Moncada actually showed that the amount of NO in the perfusion fluid coming from the endothelial cells was sufficient to completely account for the relaxation of the bioassay strips. In 1987, Ignarro published a paper in which he showed that EDRF from endothelial cells of a perfused pulmonary artery, when passed into a hemoglobin solution produced a spectral change which was the same as that produced when NO was added to the hemoglobin solution. Thus he had chemical evidence for nitric oxide being released, but his results did not, like Moncada's, show that the quantity of NO released was sufficient to account for the full relaxation by EDRF.

Of course, Viagra has made a lot of publicity for nitric oxide.

Viagra is a phosphodiesterase inhibitor. The erectile function of the penis depends on relaxation of the smooth muscles of the corpora caverno sum

due to nitric oxide, mainly coming from the NANC nerves (now called nitrergic nerves). It plays a major role in the erectile function; there are other factors too, hormones and other neurotransmitters involved. Nitric oxide apparently plays an essential role. Viagra potentiates the effect of nitric oxide by blocking an enzyme, which ordinarily inactivates the cyclic GMP, which is an intermediate in the chain of events that leads to the relaxation.

I would like to go now back to your beginnings.

My grandfather on my father's side, Fürchtgott originally, came from the Austro-Hungarian empire in 1864. He came from Nitra, then a part of Hungary, but now in the Republic of Slovakia. The family was Jewish and had some connections in Budapest. A Dr. Thomas Stern in Bratislava is presently trying to get together a history of Jewish families in Slovakia, and I've sent him material recently about our family. A member of our family may have been a Professor of Astronomy in Budapest. About six or seven years ago I tried to visit the Jewish cemetery in Nitra. According to my records, my grandfather who started a business in Charlston, South Carolina, in about 1865, went back for a visit to Nitra in about 1882. He wanted to see his relatives and to buy goods for his store. At that time, he had three small children (a girl and two boys) and he took them with him to visit his home and friends. While they were there, the two small boys died in an influenza epidemic and were buried in Nitra. This was before my father was born. They would've been my uncles, had they lived. When friends from Bratislava several years ago took me to Nitra, we found the synagogue, which was closed, and by the time we found the cemetery, it was late afternoon and it was closed too. Since then, I've met one friend from Bratislava who had visited the cemetery in Nitra more recently but couldn't find the tombstones of those children. He did find a stone tablet with lots of different names engraved, including some Fürchtgotts, probably victims of the Holocaust.

How about your mother's side?

She was born in the United States, as was her mother. Her maternal grandfather was from a region in Europe that was some times Germany, at other times Poland. He came over before the Civil War and settled in a small town, Blackville, South Carolina. He was a cobbler. He did very well; eventually he had a lot of property and also a lot of children. I don't know how my parents met but I was their second child.

How much religion was there in your childhood?

We belonged to a Reformed Jewish Temple in Charleston. I didn't finish all my religious training there because my family moved to my mother's hometown of Orangeburg, South Carolina, during the Depression. The department store in Charlston, which my grandfather and one of his brothers had started was a large and prosperous business. After my grandfather died in 1921, it was run by my father and his two brothers and during the Depression, in the late 1920s, the store began to lose money and went bankrupt close to 1930. My father started a smaller business in Orangeburg, a town of about eight thousand people. There were six or seven Jewish families in Orangeburg. They held services not in a synagogue but just in somebody's home. There was no rabbi there, except that about once a month a travelling rabbi would come by. I was not bar mitzvahed but I was confirmed when I was 15 or 16.

Robert Furchgott with his new bride, Lenore, in Charleston, South Carolina in 1942 (courtesy of Robert Furchgott).

Do you have children?

I have three children, all girls by my first wife, who died of cancer in 1983. None of them are scientist. All of them are artists. None live close by. The oldest lives in Wisconsin, the middle one in Seattle, and the youngest in Hawaii.

I'd like to ask you about your schools.

I went to primary school in Charlston and started high school there. Then I trasferred to Orangeburg. There was no discrimination in the high school. Of course, at that time, there was a great discrimination against blacks. But one didn't think about it at the time because it was an accepted part of the social scene.

I finished high school in 1933. It was during the Depression. My brother had just finished at the University of North Carolina at Chapel Hill in aeronatical engineering. My family wasn't well off financially. I knew I wanted to go into chemistry. I liked chemistry and I played with chemistry sets. The high school chemistry course was given by the basketball coach for the girls. I knew more chemistry than she did at that time. I had a good teacher in physics and math. The football coach taught them and I played football under him as well. I wanted to go to the University of North Carolina where my brother had gone but I had to go my first year to the University of South Carolina because the tuition was much cheaper for state residents. The following summer my father moved his business to North Carolina, from a cotton growing region to a tobacco growing region, and I continued my studies at the University of North Carolina in Chapel Hill. I graduated with a B.S. in chemistry in 1937.

I wanted to do graduate work in physical organic chemistry and applied to a lot of places and nothing was coming through. One of my good friends, Leslie Lane, who was not Jewish, and was second to me in the class, got an assistantship at some university in Wisconsin. At that time there was still considerable anti-Semitism and discrimination and you almost always had to indicate your religion on any application. The head of our department at Chapel Hill, Dr. Edward Mack knew of a Dr. Henry Bull who had just become Assistant Professor of Physiological Chemistry at Northwestern University Medical School and he knew Bull had an opening for graduate assistant. So I went to Northwestern where I worked toward my Ph.D. degrees as assistant in the Physiological Chemistry Department.

I took some courses with the medical students at the Chicago campus and chemistry courses at the Evanston campus.

In the summer of 1938, Henry Bull was to give a talk on his research at Cold Spring Harbor. Even at that time they had an annual Cold Spring Harbor Symposium on Quantitative Biology. The 1938 symposium was on protein chemistry. Edsall, Fruton, Astbury, Mirsky, Dorothy Wrinch, Langmuir, du Vigneaud, and many other famous people were there. These early symposia went on for almost four weeks. Sometimes there was only one lecture a day with a lot of discussion. I got free room and board because I tended the lantern slide projector at the symposium sessions. I also took part in the discussions. Langmuir talked about protein surface films, monolayers, and tried to deduce some properties of the structures of proteins from his monolayer studies. I had worked some on that subject as a graduate student and in the discussion period I voiced my disagreement with some of his conclusions. It was a very exciting time for me. After the symposium Harold Abramson, a physician-scientist, engaged me to assist in a research project for the rest of the summer at Cold Spring Harbor. He was interested in the electrophoresis of red blood cells under different conditions. Eric Ponder, Director of Cold Spring Harbor Laboratory and an outstanding researcher on red cell structure, became my mentor for my Ph.D. thesis because when I got back to Northwestern, Henry Bull encouraged me to continue the research I had started at Cold Spring Harbor. The next symposium at Cold Spring Harbor in 1939 was on hormones and metabolism and I went back to attend it and to continue my Ph.D. research on red blood cells. There was, again, a very distinguished group of speakers at the symposium, among whom were Leonor Michaelis, Fritz Lipmann and Carl Cori. I met Ephraim Shorr there and eventually I went to do postdoctoral work with him at Cornell University Medical School in New York City. By the summer of 1940, I had received my Ph.D. degree, and took part as an invited speaker, reporting on some of my research on red blood cells, at the Cold Spring Harbor Symposium of that summer on the topic of cell membranes.

When I finished my doctorate, I wanted to continue working with red cells and protein chemistry. I applied for a job in the Textile Institute in Washington. I had to go to several places to be interviewed by members of the scientific advisory board of the Institute, and then return to Washington. The head of the laboratory in Washington, Dr. Harris, said that he would like to have me there but the people, who interviewed me, came to the

The Nobel Prize winners in Physiology or Medicine with their wives and the King and Queen of Sweden in the City Hall of Stockholm on December 10, 1998. From left to right: Ferid and Carol Murad, the Queen, Maggie and Robert Furchgott, the King, and Louis and Sharon Ignarro (courtesy of Robert Furchgott).

Robert Furchgott in his laboratory, 2000 (photograph by I. Hargittai).

opinion that that there were already too many Jews in the Institute, and they decided against having me come there. It was just as well because in the end I went to Cornell, where I learned a lot in research with Ephraim Shorr on tissue metabolism, circulatory shock, physiology and pharmacology of smooth muscle, etc. Since 1940, the climate of religious discrimination has eased up almost completely in the professions.

Has the Nobel Prize changed your life?

Not a lot but some. It came at a bad time because of my wife's illness (Alzheimer's Disease) and she couldn't really enjoy it. She is now in a nursing home. Because of her condition, the past year has been a very difficult time for me. I was quite depressed. My functioning was very poor for more than a year and I turned down many invitations to give lectures. But coming back to the effect of the Nobel Prize, it's amazing how much special treatment one gets after one wins something like this. At my University they have had at least two different special banquets in my honor. One of them was a fund-raiser for research and I was the featured honoree. One of the nicest awards from the University is that the trustees have placed at my service a driver and a limousine. He brings me to work each day and takes me home. It's about an hour's drive each way.

There was a lot of controversy ...

about that Prize.

Not about your part though. Would you feel comfortable to comment on it?

I've commented on it before. I think that Salvador Moncada should've been a co-winner, without going into who might've been displaced. There can be no more than three winners of a Nobel Prize in any category in the same year.

Knowing that the Swedes try to do a thorough job, how could this happen?

I'd rather not talk too much about it. If I'd been on the award committee, I would have voted for Salvador as one of the winners. That's about as much as I can say.

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